DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

Tuesday, July 27, 2004

8:30 a.m.

ACS Conference Room
5630 Fisher Lane
Rockville, Maryland

PARTICIPANTS

Otis W. Brawley, M.D., Acting Chair
Johanna M. Clifford, M.S., RN, Executive Secretary

MEMBERS

Ronald M. Bukowski, M.D.
Bruce D. Cheson, M.D.
James H. Doroshow, M.D.
Stephen L. George, Ph.D.
Antonio J. Grillo-Lopez, M.D.
Pamela J. Haylock, RN
Maha H.A. Hussain, M.D.
Alexandra M. Levine, M.D.
Joanne E. Mortimer, M.D.
Michael C. Perry, M.D.
Maria Rodriguez, M.D.

CONSULTANT (Voting)

Ralph D'Agostino, Ph.D.

PATIENT REPRESENTATIVE (Voting)

Sheila Ross

FDA

Martin Cohen, M.D.
Richard Pazdur, M.D.
Robert Temple, M.D.
Yong-Cheng Wang, Ph.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. BRAWLEY: Good morning. I am Otis Brawley. I am a professor at Winship Cancer Institute of Emory University. I will be the Acting Chair of the Oncologic Drugs Advisory Committee for the day.

I would like to welcome everyone here and like to start out by coming the meeting to order.

The first order of business will be to introduce the members of the committee and then we will have the conflict of interest statement read.

So, if we can start off to my left with Ms. Sheila Ross, if you would introduce yourself, and as members introduce themselves, if they could mention what institution they are from.

Introduction of Committee

MS. ROSS: Thank you. Good morning. My name is Sheila Ross. I am the Washington representative for the Alliance for Lung Cancer. I am here as a patient advocate. I am also a two-time survivor of non-small cell lung cancer.

DR. GRILLO-LOPEZ: My name is Antonio Grillo-Lopez. I am a hematologist/oncologist with the Neoplastic and Autoimmune Diseases Research Institute.

MS. HAYLOCK: I am Pamela Haylock. I am an oncology nurse and a doctoral student at the University of Texas Medical Branch in Galveston, and I am the consumer representative.

DR. D'AGOSTINO: Ralph D'Agostino from Boston University, a biostatistician, consultant to the panel.

DR. GEORGE: Stephen George, also in biostatistics, Duke University.

DR. LEVINE: Alexandra Levine, hematology/oncology at University of Southern California in L.A.

DR. BUKOWSKI: Ronald Bukowski, medical oncologist, The Cleveland Clinic.

DR. DOROSHOW: Jim Doroshow, medical oncology, National Cancer Institute.

DR. RODRIGUEZ: Maria Rodriguez, hematology/oncology at M.D. Anderson Cancer Center

in Houston.

MS. CLIFFORD: Johanna Clifford, Executive Secretary to this committee.

DR. HUSSAIN: Maha Hussain, Professor of Medicine and Urology, University of Michigan.

DR. PERRY: I am Michael Perry from the University of MIssouri, Ellis Fischel Cancer Center in Columbia, Missouri, hematology/oncology.

DR. CHESON: Bruce Cheson, hematology/oncology, Georgetown University, Lombardi Comprehensive Cancer Center.

DR. WANG: Yong-Cheng Wang, FDA, statistical reviewer.

DR. PAZDUR: Richard Pazdur, Division Director, FDA.

DR. BRAWLEY: Thank you.

If Ms. Clifford could read the conflict of interest statement.

Conflict of Interest Statement

MS. CLIFFORD: Thank you. The following announcement addresses the issue of conflict of interest and is made a part of the record to

preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for appearance of a conflict of interest with the following exceptions:

Dr. Ronald Bukowski has been granted a 208(b)(3) waiver for consulting with a competitor on an unrelated matter. He receives less than 10,001 a year.

Dr. Maha Hussain has been granted waivers under 208(b)(3) and 21 USC 505(n) for owning stock in two competitors. The stocks are valued from $25,001 to $50,000, and from $50,001 to $100,000.

Sheila Ross has been granted a waiver under 21 USC 505(n) for owning stock in a competitor, valued between $5,001 to $25,000. Because her stock interests falls below the de minimis exception allowed under 5 CFR

2640.202(b)(2), a waiver under 18 USAC 208 is not required.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note that Dr. Antonio Grillo-Lopez is participating as the acting industry representative, acting on behalf of regulated industry. Dr. Grillo-Lopez is employed by the Neoplastic and Autoimmune Disease Research Institute.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment

upon.

Thank you.

DR. BRAWLEY: Thank you, Ms. Clifford.

The committee is gathered today to discuss the New Drug Application for Alimta or pemetrexed, an Eli Lilly compound proposed as a single agent treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

I would now like to introduce Dr. Richard Pazdur, Director of the Division of Oncology Drug Products, Center for Drug Evaluation & Research of the FDA to give us an introduction.

NDA 21-677, Alimta (pemetrexed)

Eli Lilly & Company

Introduction

Richard Pazdur, M.D.

DR. PAZDUR: Thank you, Otis. It is a pleasure to be here, and I welcome the participants, the members of ODAC, as well as the audience to this most interesting ODAC presentation.

I have entitled my comments "Inferiorities of Non-Inferiority Trials." I will just start off by saying I was listening to the Democratic Convention yesterday and Al Gore was talking about the 2000 election, and he said, "There are winners, there are losers, and then there is this third area," and it is kind of this third area, if I could take some statistical liberties that we are going to be talking about, and that is this whole area of non-inferiority, not positive, not negative, but some assumption of being equal.

I would like to preface today's presentation with a few comments really to focus your attention on key issues. This NDA highlights some unique challenges in developing oncology drugs regarding non-inferiority trial design and analysis.

Survival as an endpoint for regular approval has been a well-established endpoint for clinical benefit and regular approval. In oncology trials, test drugs have generally demonstrated survival improvements compared to active controls.

Alternatively, an effect on the survival endpoint may be accomplished by demonstrating a non-inferior survival effect. Non-inferiority ensures that a survival advantage, the so-called "control effect," would not be lost by a new agent. To determine the control effect, external historical information from multiple control trials is generally required.

A certain proportion of the control effect, known as the margin, should be preserved to demonstrate non-inferiority. The active control in a non-inferiority trial should have an effect that is of substantial magnitude and that can be precisely estimated with estimates relevant to the setting.

The ICHE9 guidance states that an acceptable active comparator "could be a widely used therapy whose efficacy in the relevant indication has been clearly established and quantified in well-designed and well-documented superiority trials"--and I emphasize the plurality of that word--"and which can be reliably expected

to have similar efficacy in the contemplated active control trial."

The active control, therefore, should be preferably derived from multiple studies with a large consistent drug effect suitable for a convincing meta-analysis to be performed.

Constancy assumptions must be addressed in designing a non-inferiority trial, ensuring that the active control effect should be the same as in the historical controls. These considerations ensure that the population enrolled in the historical trials is similar to the population in the proposed trial with respect to baseline characteristics, supportive care, additional available therapies, and observational frequencies.

The primary objective in the present Alimta trial was not achieved. Neither superiority nor non-inferiority to docetaxel were adequately demonstrated.

The FDA believed that Alimta's non-inferiority for overall survival cannot be demonstrated for two reasons. First, only a single

small historical study exists to estimate the docetaxel treatment effect. This study randomized a total of 104 patients, approximately 50 patients in each arm, to receive either docetaxel or best supportive care.

A second study was used in the docetaxel approval consideration. This study compared docetaxel to either ifosfamide or vinorelbine. Neither agent had a demonstrated survival effect in this setting.

This second trial failed to demonstrate an overall survival benefit associated with docetaxel, however, there was an improvement in one-year survival. Although sufficient data existed to approve docetaxel in this setting, the FDA believed that there is not a reliable and reproducible characterization of the docetaxel effect to use in a non-inferiority analysis. Constancy assumptions cannot be verified and interstudy variability is unknown.

An additional concern is the existence of crossover in the present study. Over 30 percent of

patient randomized to receive Alimta subsequently received docetaxel at disease progression. Crossover obscures the differences between treatments, hence, in a superiority trial, crossover may lead to a false negative conclusion potentially denying an active drive a marketing claim.

The use of a time to progression endpoint, an analysis occurring prior to crossover, may be preferred in settings where significant crossover is expected.

In contrast to superiority trials, crossover in non-inferiority trials may lead to a false positive conclusion. This crossover confounds our interpretation of survival since the observed survival in both arms can theoretically be attributed to the control drug, in this case docetaxel.

Similarly, data integrity problems, known as trial sloppiness, either lack of attention to details in data collection or execution may obscure the observation of differences leading to false

positive non-inferiority trials, hence, the agency has strongly recommended two trials to support a non-inferiority claim in an attempt to ascertain a true effect.

For regular approval of a drug, the sponsor must demonstrate that the drug is safe and effective in adequate and well-controlled trials. The effectiveness must be demonstrated on an endpoint that the agency believes to represent clinical benefit, usually survival, disease symptom amelioration or established surrogates for these.

The sponsor is not obligated to show that the drug is safer and/or more effective than an approved drug. Many other therapeutic areas conduct placebo-controlled trials, drug A versus placebo, ensuring that superiority can be easily demonstrated even if a comparator drug is commercially available.

It is more difficult to demonstrate superiority in an active control trial, drug A versus drug B. The test drug must possess the entire activity of the active control on the

endpoint plus an incremental addition effect to demonstrate superiority.

The agency has frequently recommended add-on trials, A plus B versus B. This design was used in the approval of Alimta plus cisplatinum in mesothelioma earlier this year.

In the add-on design, the test drug plus active control combination is compared to the active control alone or, alternatively, active control plus placebo. This design ensures that all patients receive the active treatment, yet isolates the test drug's effect.

To demonstrate superiority, the test drug must only possess an incremental advantage over the active control on the primary endpoint rather than the control effect plus an increment.

We will be asking the committee to consider this application for accelerated approval. For accelerated approval, an improvement over available therapy must be demonstrated and may utilize a surrogate endpoint "reasonably likely to predict clinical benefit."

A more favorable safety profile could constitute a "improvement over available therapy." This decision requires considerable clinical judgment, and is not merely an exercise in adding up Grade 3 and 4 toxicities in two columns and declaring a winner.

The importance of a selected toxicity in patient management, toxicity duration, and overlapping toxicity, such as concomitant neutropenia plus diarrhea, concomitant neutropenia plus stomatitis may direct your clinical opinion.

With regards to surrogate endpoints for accelerated approval in this application, the agency has used response rates of similar magnitude and duration as demonstrated in this Alimta trial for past accelerated approvals in similar disease settings.

In making a regulatory decision, we must consider all available data, a comprehensive drug evaluation including past approvals and single-arm studies. As noted, Alimta in combination with cisplatinum was approved for a mesothelioma

indication earlier this year. An improvement in overall survival advantage was demonstrated, the first for a drug in this disease.

In contrast to other accelerated approval applications that commonly use single-arm trials, the sponsor has provided a large randomized trial. Randomized trials always provide greater information.

We have comparative response rate data, we have comparative toxicity data, and we have the ability to examine time to event endpoints although we believe formal, non-inferiority analysis can neither be performed on TTP nor survival.

The sponsor is conducting large randomized trials in early lung cancer that can serve as confirmatory studies for clinical benefit if accelerated approval is granted. The statistical analysis and the design of non-inferiority trials is an evolving field and represents considerable challenges.

Non-inferiority trials are difficulty. They take considerable resources in planning,

designing, and executing trials and usually require considerable patient resources.

In conclusion, winning is always better than tieing. The demonstration of superiority is always better than that of non-inferiority. Winning moves the field forward by identifying new agents and treatments.

However, a win may not only be an efficacy improvement, but may also be a safety improvement especially in a field such as oncology where toxicity concerns may dictate treatment choices or whether a patient even receives any therapy.

However, as we would like you to discuss later this morning, this regulatory decision must be carefully weighed against the clinical relevance of any potential survival loss.

I hope these comments will focus your attention and deliberations on the essential issues presented in this application.

Thank you.

DR. BRAWLEY: Thank you, Dr. Pazdur.

Our sponsor presentation will now begin

and last over the next hour.

If I can introduce Dr. Paolo Paoletti of Eli Lilly, who will give us the introduction objectives, and if you would present the presenters as we move along.

I should add that we are going to hold all questions until after the open public hearing.

Sponsor Presentation

Introduction and Objectives of the Presentation

Paolo Paoletti, M.D.

DR. PAOLETTI: Good morning. My name is Paolo Paoletti. I am the Vice President for Lilly Oncology Clinical Research and Oncology Products. I want to thank the FDA and the members of the Advisory Board for allowing Lilly to present the data on Alimta for the treatment of second-line non-small cell lung cancer.

[Slide.]

Here is the agenda for the Lilly presentation. I will give a short introduction on the objectives of the presentation, the historical context, and the rationale for the design of the

pivotal registration trial.

Dr. Frances Shepherd, Professor of Medicine at the University of Toronto, and President of the International Association for the Study of Lung Cancer, and also principal investigator for the Phase III pivotal trial, Alimta versus docetaxel, will give the ground for the treatment of second-line non-small cell lung cancer.

Dr. Roy Herbst, the Chief of Thoracic Oncology at M.D. Anderson, University of Texas, will present the development of Alimta after the pivotal trial JMEI.

Dr. Paul Bunn, Director of the University of Colorado Cancer Center, past President of ASCO, and principal investigator for the Phase III trial Alimta versus docetaxel will present the efficacy result of the pivotal trial JMEI.

Dr. Richard Gralla, President of the Multinational Association of Supportive Care, will report the data on safety profile and patient reported outcomes for the same trial.

Finally, Dr. Bunn will give the conclusion.

[Slide.]

Additional experts from other international academic institutions are here today to answer your questions, and also experts from Lilly.

[Slide.]

In this slide, you can see the specific expertise are here to answer to your questions.

[Slide.]

The objective of the presentation is to provide evidence that Alimta is effective and safe.

We intend to show that given the superior safety results, Alimta has a better risk-to-benefit profile than docetaxel and provides benefit to patients with non-small cell lung cancer.

This is supported by, first, Alimta is a novel and effective agent in non-small cell lung cancer. Alimta has the same efficacy as docetaxel when looking at the variety of efficacy endpoint including survival, time to progressive disease,

response rate in the entire population of patients.

In addition, this efficacy is consistently present when looking at the large number of subgroups. Alimta is estimated to retain 102 percent of docetaxel benefit over best supportive care.

Alimta is superior to historical best supportive care. Alimta has an excellent safety profile and superior safety results when compared to docetaxel. Therefore, Alimta offers an effective and safer second-line treatment option for patients with non-small cell lung cancer.

[Slide.]

We propose the following indication. Alimta as a single agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy, and at the dose of 500 mg/m2 i.v. with a 10-minute infusion at day 1 of each 21-day cycle, and to control toxicity, oral folic acid at the daily dose of 350-1,000 microgram and vitamin B12 at the dose of 1,000 microgram every 3 cycles

given IM, dexamethasone 4 mg/bid on day minus 1, day of the treatment, and day plus 1.

[Slide.]

In this slide, I summarize the historical context and the rationale for the statistical design when the pivotal trial JMEI was initiated.

Alimta showed consistent activity in non-small cell lung cancer in seven Phase II trials as a single agent or in combination with platinum agents both in first- and second-line.

This activity compares well with data from other commonly used regimens. Folic acid and B12 interventions significantly improve the safety profile of Alimta, however, the magnitude of this intervention was not completely known at the time of the initiation of the Phase III pivotal trial JMEI.

It was decided to proceed with the Phase III trial in second-line to offer a better alternative treatment.

[Slide.]

The trial, as Dr. Pazdur was saying,

presented several design challenges and limitations, but we decided to run a head-to-head trial Alimta versus docetaxel.

We wanted to run a global clinical trial to support global registration. Best supportive care in second-line treatment of non-small cell lung cancer was considered not practical because of the presence of the docetaxel as an approved agent in second-line treatment and not feasible in the United States and in many countries in Europe.

Combination chemotherapy was considered not appropriate especially in this second-line setting. Docetaxel was approved in second-line non-small cell lung cancer primarily based on the result of the trial TAX 317B where superior survival over best supportive care was demonstrated in 55 patients treated at the dose of 75 mg/m2.

Survival was selected as the primary endpoint, however, we acknowledge the presence of limited historical data on the effect of docetaxel. Moreover, a pure equivalency trial would require more than 4,000 patients.

[Slide.]

The JMEI is a global registration trial, and we discussed the statistical design with both FDA and the European Regulatory Agency. Sample size of 520 patients allows for testing of superiority. With the assumption of superiority, this sample would also allow for testing non-inferiority. The hazard ratio was the basis to compare treatment arms for survival.

The protocol specified superiority testing, as well as testing 10 percent fixed margin for non-inferiority. This margin was agreed upon with the European Agency. We always believe this was a very conservative matching. Indeed, the magnitude of the effect of folic acid supplementation on toxicity was not known at the time. Thus, safety advantages of Alimta were not considered in the definition of this match.

Before unblinding the data, we included the percent retention method for non-inferiority in the statistical analysis plan. The FDA suggested for the evaluation of Alimta the retention of the

effect of docetaxel, docetaxel versus best supportive care.

The FDA used this methodology to approve docetaxel in breast cancer and capecitabine in colon cancer. Rothmann and co-authors published percent retention method in January 2003, and the details of the percent retention analysis were included in the statistical analysis plan before unblinding the data and before any analysis was undertaken.

[Slide.]

This slide shows the Alimta lung cancer submission timeline. The first patient was enrolled on March 20, 2001. The last patient was enrolled on February 6, 2001. The Final Statistical Analysis Plan was approved on January 24, 2003.

Unblinding of the analysis and the data occurred on January 30, 2003. U.S. fast track designation for second-line treatment of non-small cell lung cancer was granted on July 23, 2003. Non-small cell lung cancer submission was filed in

November 4, 2003 in the U.S., and in July 2003 for Europe.

In June 22nd of this year, the European CHMP, the regulatory agency, gave a positive opinion for both second-line non-small cell lung cancer and mesothelioma.

[Slide.]

Alimta has already shown to be an active agent in cancer. In fact, Alimta, in combination with cisplatin, was approved on February 4, 2004 for the treatment of mesothelioma in the United States.

This slide shows the survival curve. You can see that the combination Alimta plus cisplatin has a median survival of 12.1 months, while cisplatin alone has a median survival of 9.3 months. The difference was statistically significant at P of 0.02.

[Slide.]

Based on the evidence of the next presentation, we believe that Alimta merits the approval for the treatment of second-line non-small

cell lung cancer for the following reasons.

Seven Alimta Phase II studies in first-and second-line non-small cell lung cancer show consistent evidence of activity within the range of activity of other agents currently available.

From this large Phase III randomized clinical trial in second-line non-small cell lung cancer, Alimta showed consistent similar clinical efficacy when compared to docetaxel in all primary and secondary endpoints and in all subgroup analyses.

Alimta is better than historical best supportive care. Moreover, Alimta is significantly better for clinically relevant toxicity when compared to docetaxel.

Only docetaxel is approved for second-line treatment today, and there is a need for more second-line treatment option.

[Slide.]

Alimta is an effective drug for the treatment of second-line non-small cell lung

cancer, and it has a better risk-to-benefit profile when compared to docetaxel.

As you hear the rest of our presentation and that from the FDA today, please keep into consideration the following points:

Docetaxel at the dose of 75 mg has shown activity across several studies in second-line of non-small cell lung cancer after the pivotal trial TAX 317B, however, its use is limited by its toxicity. The results in 288 patients receiving docetaxel in the JMEI pivotal trial confirms docetaxel's survival effect.

As I mentioned before, docetaxel was approved based on limited data, hence, the imprecision of the effect of docetaxel made non-inferiority design and related analyses very challenging.

This context, together with the lack of feasibility to conduct placebo-controlled trial once the drug is approved makes further advancement in drug development very difficult.

Although post-study treatment, inevitable

in the United States, may confound survival result, the analysis from the pivotal trial JMEI suggest that such a confounding effect is unlikely.

In conclusion, I respectfully request that the members of this advisory board evaluate the data in second-line treatment of non-small cell lung cancer considering the overall efficacy and safety that will be presented.

Now, Dr. Frances Shepherd will give the background for the second-line treatment for non-small cell lung cancer.

Background on Non-Small Cell
Lung Cancer Second-Line Treatment
Frances A. Shepherd, M.D.

DR. SHEPHERD: Thank you very much, members and guests.

[Slide.]

In 1997, the ASCO Guidelines stated that "there is no current evidence that either confirms or refutes that 2nd-line chemotherapy improves survival in non-small cell lung cancer."

This conclusion was reached only seven

years ago because, at that time, only single-arm, Phase II trials were available. However, several trials of the third-generation agent docetaxel suggested that this agent might be appropriate to study further in randomized Phase III trials.

[Slide.]

In the first trial initiated, the TAX 317 study, patients previously treated with at least one platinum-based regimen were stratified based on their ECOG performance status, 0.1 versus 2, and on their best response to prior chemotherapy.

They were randomized to receive either docetaxel 100 mg/m2 or best supportive care. Routine safety monitoring revealed 5 or 10 percent early toxic deaths in the chemotherapy arm. Therefore, after discussion with the principal investigators and the FDA, the docetaxel dose was reduced to 75 mg/m2 for the second half of the study.

The sample size was maintained at 200 patients as originally planned due to the difficulty in accruing patients to this study

because of the best supportive care arm.

[Slide.]

The overall response rates to docetaxel 100 and 75 mg/m2 were both 6 percent. Time to progressive disease was 2.8 months for patients treated with docetaxel 75 mg compared to only 1.6 months for best supportive care. Median survival was significantly longer for docetaxel 75 mg treated patients at 7.5 months compared to only 4.6 months for best supportive care. One-year survival was 3-fold higher for docetaxel patients.

[Slide.]

Survival is shown graphically in this slide for the second half of the trial at docetaxel 75 mg/m2, the FDA approved dose. Survival was significantly longer for patients treated with docetaxel with a log-rank p-value of 0.01. One-year survival was significantly higher with a chi-square p-value of 0.003.

[Slide.]

This is a very important slide to concentrate on. In this trial, patients must have

received one platinum-containing regimen, but could have received more than one regimen before entering the trial.

As you can see from this slide, the numbers of patients unfortunately are small, and these must be considered exploratory subset analyses, however, they suggest that patients treated with docetaxel after two or more regimens derived absolutely no survival benefit from the treatment as compared to best supportive care alone.

The entire survival benefit of the trial came from the administration of docetaxel in the true or strictly defined second-line setting.

[Slide.]

The second large trial was the TAX 320 trial and was performed in the United States where a best supportive care trial could not be conducted.

In this trial, patients were stratified by their best response to platinum-based therapy and performance status, and were randomized to receive

docetaxel 100 mg/m2 or docetaxel 75 mg/m2, or a comparator of vinorelbine or ifosfamide. This was largely vinorelbine.

[Slide.]

The overall response rate was 11 percent for patients treated with docetaxel 100 mg, and 7 percent for patients in the 75 mg group. Both of these response rates were significantly higher than the 1 percent response rate noted in the control group with p-values of 0.001 and 0.036.

There was no difference in median or overall survival among the three treatment arms, however, the one-year survival rate of 32 percent for patients treated with docetaxel 75 mg, the FDA-approved dose, was significantly better than the 19 percent one-year survival rate of patients treated with vinorelbine or ifosfamide. Chi square p-value for this is 0.05.

[Slide.]

This is shown graphically on this slide where you will see the survival curve separating in the latter part.

[Slide.]

The FDA-approved label for docetaxel 75 mg reports Grade 3/4 neutropenia of 65.3 percent, Grade 3/4 infection of 10.2 percent, and using a very stringent definition, febrile neutropenia rate of 6.3 percent.

Although Grade 3 and 4 diarrhea and neurotoxicity are rare at this dose of docetaxel, lesser grades of both of these toxicities may be distressing to patients. Similarly, alopecia, although never life-threatening, may have a major negative emotional impact on both men and women.

[Slide.]

Quality of life and symptom control was measured in both the TAX 317 and 320 trials. Pain was significantly better controlled in the 317 trial, and this was not because of increased opioid use. You can see from this slide that opioid use was the same at study entry in both arms of the trial, however, significantly fewer patients treated with docetaxel required additional opioids and significantly fewer patients required the

introduction of new opioids.

[Slide.]

Weight loss was measured closely, and you will see that in the TAX 317B trial, 25 percent of patients treated with best supportive care had weight loss greater than 10 percent compared to only 2 percent of patients treated with docetaxel. Weight loss greater than 10 percent was seen in only 5 percent of patients treated with docetaxel 75 mg/m2 in the 320 trial compared to 8 percent for vinorelbine patients.

[Slide.]

Treatment was not at the expense of quality of life or performance status. Indeed, performance status improved during the study for patients treated with docetaxel whether measured at initiation, across the cycles, or at the last treatment.

[Slide.]

In summary, these landmark trials showed that second-line chemotherapy prolonged survival in non-small cell lung cancer. It also improved

symptom control and does not have a negative effect on quality of life or performance status.

These trials led to the approval of docetaxel 75 mg/m2 for the second-line treatment of non-small cell lung cancer in 1999.

[Slide.]

In 2003, the revised ASCO evidence-based guidelines recommended docetaxel for patients with non-small cell lung cancer who have progressed on first-line platinum-based therapy.

[Slide.]

In summary, the body of evidence shows that patients derive benefit from second-line treatment of non-small cell lung cancer with docetaxel. However, better tolerated or more effective alternatives are needed.

Finally, docetaxel is being used more frequently in the first-line setting and no options are currently available for patients who are treated first-line with docetaxel-containing regimens.

As docetaxel is the only approved agent

for the second-line treatment of non-small cell lung cancer, additional options are required.

Dr. Roy Herbst will now discuss the development of Alimta.

Alimta Development

Roy Herbst, M.D., Ph.D.

DR. HERBST: Good morning, panel members and guests. My name is Roy Herbst from the M.D. Anderson Cancer Center. Our group and myself personally have worked with this drug both in the front and second-line setting in non-small cell lung cancer.

[Slide.]

My purpose this morning is to provide some background information regarding this novel antifolate and to share supporting evidence that Alimta has activity in patients with non-small cell lung cancer, as well as providing clinical benefit.

[Slide.]

First, a word about the structure. As you can see, Alimta is very similar to folic acid, but really it is quite a unique and novel compound.

You can see two circles areas on the slide. The N-10 nitrogen has been replaced by a methylene group, and most importantly, the pyrrolo-pyrimidine ring circled makes this structurally different from other antifolates. That is important because it gives it some very unique qualities as I will talk about in the next slide.

[Slide.]

Shown here is the mechanism of action of this drug, which is a multi-targeted antifolate. As shown in the left, the Alimta enters the cell by reduced folate carriers. Once inside the cell, it is polyglutamated. This potentially allows it to be stored in the cell for higher intracellular concentration.

You can then see that it blocks three different enzymes involved in folate metabolism - TS, DHFR, and GARFT. There is also the potential for this drug to be active in MTAP [ph] efficient cells. This makes it potentially more active, as well, at any cell that might upregulate any one of these different enzymes.

[Slide.]

Activity has been across a wide spectrum of tumor models. Today, we will focus on lung cancer. Here, you can see four non-small cell lung cancer cell lines with activity in the nanomolar range. There is also evidence here of a lung cancer xenograph, and you can see the drug is quite active, as well.

[Slide.]

What about clinical experience? First, the front-line experience. Shown here are two studies that looked at Alimta before vitamin supplementation in patient with non-small cell lung cancer, compared to several studies with docetaxel also in the front-line setting.

The important thing to notice here is that the activity, both based on response rates in the 20 percent range and the median survivals, from 7 to 9 months, is quite consistent with what one would expect for docetaxel or, in fact, most of the third-generation chemotherapeutics that we now use for non-small cell lung cancer.

[Slide.]

Activity has also been seen, and quite favorable toxicity, in combination with platinum, which, of course, is the way we treat lung cancer in the front-line setting.

Shown here are four studies, two using cisplatinum, two using carboplatinum, and again you can see in these Phase II studies, response rates that are quite similar to other agents in this setting, in one case in the 40 percent range, median survivals between 8 and 10 months, in fact, 13.5 months in our M.D. Anderson study, and one-year survivals are quite good. This drug clearly has activity with platinum in the front-line setting of lung cancer, as well.

[Slide.]

Going into the randomized trial that you are about to hear about, this was the Phase II experience, the study from Smit and colleagues, 79 patients. This is a refractory group of patients with non-small cell lung cancer. One hundred percent of these patients were refractory within

three months, and importantly, it's an especially bad group because 66 percent were refractory within one month.

You can see that this drug demonstrates a clear response rate of 8.9 percent with a median survival of 5.7 months, and a one-year survival of 23 percent. There is clearly activity based on this trial in the second-line setting, and we will hear more about this, of course, today.

[Slide.]

Now, what about safety? As with most antifolates, the primary toxicity of this drug is hematologic. Early data showed that high homocysteine levels, a surrogate for functional folate or B12 deficiency, correlated with high levels of toxicity.

So, a decision in development was made early on to supplement all patients with folic acid and vitamin B12 when they received this drug. This resulted in decreased toxicity with no detrimental effect on efficacy.

[Slide.]

I show one slide here. This is basically showing a group of patients, 246, without vitamin B12 and folate supplementations, single agent administration, or 220, who did receive supplementation.

Shown on the left are all the toxicities lumped together that I am going to show in this slide. You can see in the white before, and in the green after, with a significant improvement.

Then, breaking that up into the top three, you can see Grade 4 neutropenia is significantly reduced, Grade 3/4 diarrhea also significantly reduced, and at least in this Phase II experience, you can see toxic death rate is zero, and then we are seeing when the supplementation was given.

[Slide.]

So, in summary, Alimta has shown activity in non-small cell lung cancer as a single agent, both in the first- and second-line setting, in combination with platinum agents in the first line.

The safety has been well characterized. The toxicity is significantly reduced after adding

folic acid and B12, and a very low incidence of neutropenia, febrile neutropenia, and other non-hematologic toxicities.

I can personally say, both for my group and myself, this has been our experience, as well.

Based on these results, a pivotal Phase III study in the treatment of second-line non-small cell lung cancer was indicated, and Dr. Paul Bunn will now present those data.

Thank you.

Clinical Efficacy from the Pivotal Study JMEI

Paul Bunn, M.D.

DR. BUNN: Good morning, Dr. Brawley, ODAC members, and guests.

[Slide.]

As one of the principal investigators, I will review the results of the pivotal trial JMEI, which was a head-to-head comparison of Alimta to docetaxel in the second line treatment of patients with advanced non-small cell lung cancer.

[Slide.]

I will begin this presentation with the

study design and patient demographics. The results of the primary endpoint survival will be given with a detailed discussion of the survival result and comparison with docetaxel and historical best supportive care with and without adjustment in a Cox model.

Following this discussion, I will review the results of the secondary efficacy endpoints and a brief discussion of the effect of third line therapy. Because efficacy cannot be considered in the absence of toxicity, I will give a brief overview of toxicity, and then Dr. Gralla will review the safety results and patient reported outcomes in detail. Then, I will wrap up with a few concluding remarks.

[Slide.]

After stratification for known prognostic factors including performance status and stage, as well as other possible prognostic factors listed, patient were randomized to Alimta 500 mg/m2 I.V. day 1 every 21 days or docetaxel 75 mg/m2 day 1 every 21 days.

The 283 patients randomized to Alimta received B12 and folic acid supplementation and dexamethasone was given to prevent skin rash.

The 288 patients randomized to receive docetaxel received dexamethasone according to the label.

[Slide.]

The primary study endpoint was survival. This survival endpoint is expressed as a hazard ratio of Alimta to docetaxel with a 95 percent confidence interval.

Secondary endpoints included progression-free survival, time to tumor progression, response rate toxicity and patient reported outcomes as measured by the Lung Cancer Symptom Scale.

[Slide.]

Of course, these endpoints were assessed in one of two populations, intention to treat and randomized and treated. The primary endpoint survival, as well as all other time to event variables were assessed on an intent to treat

population. This population included all randomized patients regardless of therapy.

The toxicity endpoints were evaluated on randomized and treated population. This group included randomized patients who received at least one dose of treatment.

[Slide.]

Important inclusion and exclusion criteria included histologic or cytologic diagnosis of Stage III or IV non-small cell lung cancer. All patients had progressed after at least one prior chemotherapy treatment, but not more than one prior chemotherapy treatment for metastatic disease. Prior adjuvant and neoadjuvant therapy was allowed.

Patients had performance status 0 to 2 and adequate organ function. Active brain metastases, severe peripheral neuropathy or significant weight loss were not allowed. Uncontrolled pleural effusions and prior docetaxel was not allowed. Prior paclitaxel was allowed and prior platinum was not required.

[Slide.]

The most important prognostic variables, performance status and stage, were well balanced between the arms. The less important variables, such as age and gender, there were minor but nonsignificant differences. Histology and pre-treatment homocysteine levels were well balanced.

[Slide.]

There were no differences in the fraction of patients responding to initial chemotherapy or the fraction with early relapse after prior treatment.

The two groups had no relevant differences in prior chemotherapy in terms of taxane or platinum exposure.

[Slide.]

In both groups, dose intensity was well preserved with a similar number of patients receiving at least 4 cycles of therapy and a median of 4 cycles of therapy in both arms. The percent of the planned dose intensity and dose delays were similar. There was a significant increase in dose

reductions in the docetaxel arm.

[Slide.]

Of course, survival is so important in the primary endpoint and the unadjusted Kaplan-Meier survival curves for Alimta and docetaxel were overlapping and crossed several times. The median survival times are 8.3 months and 7.9 months, favoring Alimta.

The one-year survival rates was 29.7 percent in both arms. The unadjusted hazard ratio was 0.99 in favor of Alimta. The 95 percent confidence interval was 0.82 to 1.2. This hazard ratio and confidence interval did not show superiority, nor rule out a 10 percent margin.

[Slide.]

In order to more fully understand the survival implications of Alimta relative to both docetaxel and to best supportive care, the data must be put in the context of this and other studies.

Percent retention analysis is a means of estimating the amount of benefit of docetaxel over

best supportive care that is retained by Alimta. This analysis, as you have heard from Dr. Paoletti, was not in the original protocol, but was prespecified in the statistical analysis plan prior to unblinding and prior to data analysis.

The retention analysis was based on the results of TAX 317B, which was docetaxel 75 mg/m2 versus best supportive care. This analysis takes into account variability within the studies and allows for comparison of Alimta to best supportive care.

An important assumption of the percent retention analysis is comparability of populations and results between TAX 317 and JMEI. This allows for the assumption that if the best supportive care arm were to be included in JMEI, its survival curve would have been similar to that seen in TAX 317.

[Slide.]

For the most important prognostic factor, such as performance status and stage, populations in TAX 317 and JMEI were very similar. There were less important factors, such as age and gender,

there were minor differences, but overall, the pre-treatment characteristics make the populations appear comparable.

[Slide.]

Looking at the outcome of the 75 mg/m2 docetaxel arms in both TAX 317B and in JMEI, shown here, shows the results are very similar. The Kaplan-Meier survival estimate of docetaxel 75 mg/m2 from TAX 317 is shown in green and JMEI in blue. This outcome confirms the finding of TAX 317B for docetaxel.

[Slide.]

Once the populations are shown to be comparable, then the percent retention analysis allows for comparison of survival between TAX 317B and JMEI.

Superimposing the Alimta result of JMEI, which is the yellow curve I just added, it is evident the result is similar to docetaxel 75 mg/m2 from both 317B, the prior study, and the current study JMEI. This finding shows that Alimta is equivalent to docetaxel 75 mg/m2.

Now, adding in the best supportive care result, in white, strongly suggests the superiority of Alimta to best supportive care. The hazard ratio of Alimta to best supportive care is 0.55 with a 95 percent confidence interval that does not overlap 1, 0.33 to 0.9, the p-value is 0.019.

[Slide.]

Another way to understand the survival results, which are real, and the confidence interval around these results is to compare hazard ratio and confidence interval in the trial results.

Shown in yellow are the actual study results showing an unadjusted 0.99 hazard ratio, a 95 percent confidence interval of 0.82 to 1.2. For reference, the percent retention of docetaxel's benefit over best supportive care is shown below the line.

For the actual data, the hazard rate of 0.99 represents retention of 102 percent of docetaxel's benefit over best supportive care. A hazard ratio of 0.82 represents 150 percent retention, and so forth.

If we want to determine whether Alimta has benefit over best supportive care, we can calculate the hazard ratio if the percent retention were zero, indicating that best supportive care and Alimta were the same. In this case, the hazard ratio of Alimta to docetaxel would be 1.33.

Since the upper limit of the hazard ratio was 1.2, we can be quite confident that Alimta is better than best supportive care.

If we want to determine the hazard ratio if Alimta retained at least 50 percent of the benefit of docetaxel, the hazard ratio would need to be less than 1.21 for 95 percent confidence, and again this criteria was met.

If the upper limit of the 95 percent confidence interval was less than 1.11, then, Alimta would have been within 10 percent of docetaxel as originally requested by the European Regulatory Group. As shown, it did not reach this value. However, after reviewing the totality of the evidence, the European Authorities have recommended approval.

Alimta would have been declared superior to docetaxel if the upper limit of the 95 percent confidence interval had been less than 1. The result did not reach this threshold of superiority.

[Slide.]

Since not receiving therapy can affect non-inferiority analyses, the ICH Guidelines recommend that analyses of non-inferiority performed percent retention calculations on both an ITT, as well as the randomized and treated RT population.

This table shows the calculation from both populations. For the ITT population, Alimta retained 52 to 150 percent with a p-value for 50 percent retention of 0.047.

For the RT population, Alimta retained 58 to 168 percent with a p-value for 50 percent retention of 0.036.

These data support retention of docetaxel survival benefit by Alimta.

[Slide.]

As a prespecified secondary analysis, a

Cox multivariate regression analysis was performed with these 7 prespecified prognostic factors in the model. These factors included stage, performance status, time since last therapy, response to prior therapy, prior taxane, prior platinum, and number of prior chemotherapies.

[Slide.]

The results from this model showed that three factors predictive for survival - Performance Status 2, time since last chemotherapy less than 3 months, and Stage IV, all predictive for a worse survival outcome.

[Slide.]

This slide shows the adjusted survival hazard ratio on a similar number line. The actual data is represented in yellow. The hazard ratio was 0.93 with a 95 percent confidence interval of 0.76 to 1.13. The p-value for the 10 percent fixed margin was p equals 0.051.

The difference between the upper limit of the confidence interval 1.13, and the prespecified 10 percent fixed margin 1.11, translates into

approximately 3.6 days difference.

[Slide.]

This slide demonstrates subgroup analyses unadjusted and adjusted for known or potentially important prognostic factors for JMEI.

In most instances, relative subgroups, there were no appreciable treatment effect differences. For Performance Status 2 patients, the hazard ratio favored Alimta, but in this case, the sample was small, and the result was not statistically significant.

For no prior platinum, the apparent differences in the adjusted hazard disappeared when imbalances important to other factors were taken into account.

These data provide confidence that the observed results were consistent across all subgroups and that the results could not be explained by a large benefit within any particular subgroup.

[Slide.]

We will now review the secondary endpoints

of progression-free survival, time to progression, tumor response, and toxicity. In addition, I will provide an exploratory data on possible confounding effect of post-study chemotherapy.

[Slide.]

Shown is the Kaplan-Meier estimate for progression-free survival in intent to treat population. It difficult to see that there is two curves here because they are so overlapping, but there are two distinct curves with a median progression-free survival of 2.9 months in both arms.

The hazard ratio was 0.97, slightly favoring Alimta, with a 95 percent confidence interval of 0.82 to 1.16.

[Slide.]

This is the Kaplan-Meier estimate of the time to tumor progression for JMEI. Again, the curves overlap considerably with a median time to tumor progression of 3.4 and 3.5 months for Alimta and docetaxel respectively.

The hazard ratio was again 0.97, with

confidence intervals of 0.8 to 1.17.

[Slide.]

A review of chemotherapy given after this study showed that more patients on Alimta received any chemotherapy. Not surprisingly, docetaxel, which is the only approved drug, was given more frequently after progression on Alimta despite the evidence you have heard that it provides no benefit in this setting.

Receipt of docetaxel does represent a crossover of sorts. As expected, patients on docetaxel received more gemcitabine, more vinorelbine, and more gefitinib, as well as more other chemotherapy.

Of course, you will recall that gefitinib is the only agent for which there is any evidence for survival effect in third-line non-small cell lung cancer.

[Slide.]

To further understand the post-study treatment effect, an analysis was performed to look at the type of post-study therapy and its potential

effect on survival. Of course, all of these are retrospective and are subject to great bias, which we can discuss later.

Patients who received post-study therapy lived longer than those who did not, not surprisingly, regardless of the nature of that therapy or the study arm.

Patients on Alimta who received post-therapy docetaxel did numerically worse than those who received other post-treatment study, such as gemcitabine or vinorelbine.

Patients on the docetaxel arm who received post-therapy docetaxel actually had numerically better survival than those receiving docetaxel after Alimta. This post hoc analysis does not suggest any crossover effect or post-study effect of docetaxel treatment.

[Slide.]

In fact, this slide shows the distribution of survival after progressive disease by treatment arm, Alimta versus docetaxel. A higher proportion of patients on the Alimta arm received docetaxel,

and a higher proportion of patients on docetaxel received other therapies.

The median survival was 4.5 months in both arm. This comparison suggests there is no difference between salvage therapies in the two arms.

Assuming that patients with progressive disease have similar prognoses in the groups, this comparison implies the crossover to docetaxel in the Alimta arm did not affect any conclusion regarding survival.

[Slide.]

Investigators determined the best response in the study according to South West Oncology Group criteria. The response rate between the arms was virtually identical, 9.1 for Alimta and 8.8 for docetaxel, respectively.

Stable disease was seen in about 46 percent of patients on each arm. These data are consistent with the previously published data using both docetaxel and Alimta in this setting.

Because all efficacy parameters were

equivalent, much of the clinical benefit of Alimta relates to toxicity, so the toxicity analysis, of course, becomes important.

[Slide.]

This table provides a brief overview of significant toxicity differences regardless of causality. Alimta was associated with significantly less Grade 3/4 neutropenia, less febrile neutropenia, less infection with neutropenia, and less diarrhea.

There were also significantly less clinically relevant alopecia of all grades.

Alimta treatment was associated with significantly more ALT elevations, 2.6 percent versus 0.4 percent.

[Slide.]

In conclusion, the results of JMEI demonstrate that Alimta afford efficacy benefits for patients with non-small cell lung cancer undergoing treatment after progression with prior chemotherapy.

The survival result is similar to that of

docetaxel with a hazard ratio of 0.99. This hazard ratio translates into 102 percent retention of docetaxel's benefit over best supportive care.

The results are internally consistent across subgroups. In JMEI, there is no evidence of an effective crossover or other post-study chemotherapy effect.

The survival results robustly support Alimta's superiority to historical best supportive care.

In addition to the survival endpoint, all secondary endpoints, including response, time to progression, progression-free survival affirm Alimta's activity and benefit to this group of patients.

Finally, the safety profile of Alimta, which Dr. Gralla will review in detail, is clearly superior to docetaxel.

Now, I would like to invite Dr. Richard Gralla to review symptom and safety results from Study JMEI.

Safety Profile from the Pivotal Study JMEI

DR. GRALLA: Thank you, Dr. Bunn, and good morning.

[Slide.]

In considering second-line treatment in any patient with advanced lung cancer, both physicians and patients also regard the safety or toxicity of an agent with great concern.

At the same time, all wish to preserve the efficacy benefits of treatment including symptom control and to do so with fewer potential risks from treatment.

[Slide.]

Recognizing that significant patient reported outcome advantages, including pain control, were seen with the docetaxel when compared with supportive care, as Dr. Shepherd discussed with TAX 317 trial, it was important to assess prospectively this efficacy parameter in the current trial.

The study was designed to evaluate the impact of symptoms as measured by the average

symptom burden parameter of the LCSS instrument. Dr. Bunn outlined briefly the significantly lower toxicity profile with Alimta, which I will discuss in greater detail in a few minutes, but it is crucial to ascertain that the safety advantages were not achieved at the expense of the decrease in symptom control as expressed by patients.

[Slide.]

PRO, or patient reported outcome evaluations, are best conducted when using previously validated instruments. The LCSS has good published psychometric properties and was selected for prospective use in this trial for several reasons.

It is demonstrated high patient and observer acceptability, it was designed specifically for randomized comparative clinical trials, and was used in the docetaxel TAX 317 and 320 trials.

Patients completed the instrument weekly, allowing 85 percent of the patients to be included in the PRO evaluation.

Two major questions are associated with PRO evaluation. First, are the quality of life instruments used sensitive enough to reflect changes that patients experience, and, second, is there value in receiving second-line chemotherapy in terms of symptom relief and quality of life advantages?

Does the magnitude of response, major response versus stable disease versus progressive disease predict the degree of benefit expressed by patients?

[Slide.]

This slide shows the patient reported results displayed by the objective response category achieved. For this analysis, the results of both the Alimta and docetaxel arms were combined.

As can be seen, major response was associated with the greatest patient expressed benefit, the green bars, while a lesser impact, but still a positive result, was reported by those patients in whom stable disease, the magenta bars,

was their best response.

Of note is the fact that over 50 percent of patients had either a major response or stable disease in this trial, and that these groups reported symptomatic benefits as seen on the slide.

In light of the PRO benefits overall in the trial, and with the significantly lower toxicity on the Alimta arm, it is important to see that the response related symptomatic benefits were preserved with the less toxic Alimta regimen.

[Slide.]

This slide shows the evaluations for patients by randomized treatment arm and examines the results seen in those patients with major response or stable disease.

The bar graphs represent the six general and thoracic symptoms evaluated in the LCSS and the average symptom burden index, or ASBI. It is clear that these results show similar symptom amelioration for each treatment arm in these lung cancer related symptom areas.

[Slide.]

In all new agent evaluation, efficacy and safety are the main considerations. Given the similar efficacy endpoints in terms of survival, response, and patient reported outcomes found with both agents in this large randomized trial, safety issues are of marked importance when considering therapeutic index differences between the agents.

To place the overall safety profiles for second-line treatment in context, it is useful to review briefly the safety findings of the currently available second-line agent docetaxel.

[Slide.]

The docetaxel arms at 75 mg/m2 from the TAX 317 and 320 trials, which Dr. Shepherd outlined in her presentation, are seen on this slide.

When one concentrates on marked toxicities, as expressed as a percentage of patients experiencing Grade 3 or 4 levels of toxicity, it is clear that neutropenia is the primary concern occurring in the majority of patients. In fact, as originally designed, the amount of docetaxel given in TAX 317 had to be

lowered during the study to 75 mg/m2 because of undue toxicity.

Nonetheless, even at this dose, nearly two-thirds of patients still experienced marked or severe neutropenia. Physicians remain particularly concerned with the high degree of this potentially life-threatening toxicity.

While patients and physicians appreciate the modest benefits of docetaxel, concerns with neutropenia and its complications have led to the frequent need for growth factor injections and alterations of doses and schedules.

[Slide.]

An overall view of the safety in the JMEI trial is seen in this slide. The table shows the incidence of the most serious toxicity, death, serious adverse events or SAEs, and finally, any adverse event called the treatment emergent adverse event, or TEAE.

As can be see for any of these parameters, a higher rate of adverse events was found in this study with the docetaxel arm.

When one looks at either the serious adverse events affecting a minority of patients, or the treatment emergent adverse events affecting most patients, significant differences favoring the Alimta arm are found when the results are evaluated for events that are drug related.

[Slide.]

Of course, the toxicity outcome of greatest concern with any drug is death. As seen in this slide, while the number of deaths during the study are relatively similar between the two treatment arms, fewer deaths are seen in total on the Alimta arm, and in the important categories of study drug related deaths and lung cancer related deaths.

[Slide.]

When examining adverse events, any toxicity can be relevant, but major toxicity, that is, Grade 3 and 4, is of greatest concern and deserves our focus.

Clearly, an approach that lessens toxicity from the marked Grade 3 and 4 categories to Grades

1 and 2 would have the same overall toxicity percentage, but by lessening the severity would be a major benefit. All drugs have side effects, the severity of these side effects is a crucial issue in patient management and in the assessment of toxicity in this trial.

[Slide.]

This slide is the first of several summarizing laboratory-based major toxicities from the current Alimta versus docetaxel randomized trial as displayed as Grade 3 and 4 level of toxicity.

As expected, the most commonly occurring laboratory-measured side effect was neutropenia. Of note is the finding that there was a markedly different occurrence of this toxicity depending on the treatment arm.

Not only was there a highly significantly different rate of neutropenia, favoring those patients randomly assigned to Alimta, but the related life-threatening toxicity of febrile neutropenia occurred far less often in the

Alimta-treated patients affecting fewer than 2 percent.

Not surprisingly, documented infection rates were lower in those patients receiving Alimta with no occurrences found on this arm of the trial.

Now, stepping away from the statistical analysis at this point and placing it in a clinical context, these results mean that 1 of every 8 patients in this study, randomized to docetaxel, had febrile neutropenia, while this life-threatening toxicity occurred in less than 1 of every 50 patients on Alimta.

The only laboratory area in which a significantly higher side effect rate was seen with the Alimta, was in the hepatic transaminase ALT. Fortunately, this degree of elevation was uncommon, occurring in fewer than 3 percent of patients.

[Slide.]

In general, rates of non-laboratory side effects were relatively low in this study. Nonetheless, the distressing but not life-threatening side effect alopecia occurred far

less often in patients receiving Alimta.

Additionally, a significantly different rate of serious diarrhea was found again favoring Alimta.

Thus, when considering both laboratory and non-laboratory events, threatening overlapping toxicities, such as neutropenia and diarrhea, were significantly reduced by the use of Alimta.

[Slide.]

When one looks at the occurrence of all serious laboratory toxicities, that is, Grade 3 and 4, by treatment regimen, it is clear that Grade 3 toxicities occurred in only about half as many patients randomly assigned to the Alimta arm, and that Grade 4 toxicities were markedly lower in patients on that arm.

[Slide.]

During the trial, anemia was reported by about 7 percent of patients on either arm of the study. This could be related to the chemotherapy or to anemia associated with the lung cancer itself. Overall, physicians elected to transfuse

or to give erythropoietin to between 22 percent and 24 percent of patients with no significant differences between treatment arms.

With markedly lower drug-induced neutrophil counts on the docetaxel arm, 7 times as many of these patients were given granulocyte-stimulating growth factors, again a highly significant difference.

[Slide.]

The advantages in non-laboratory toxicities are perhaps best illustrated when looking at serious toxicities of any cause. The more minor toxicity grades 1 an 2 are similar between the treatment arms, however, when one reviews the more serious toxicity grades, important differences are clear.

Grade 3 toxicity rates approach statistical significance. In Grade 4, the most marked toxicity category, a third fewer patients on the Alimta arm had this rate of serious toxicity a statistically significant difference between the treatment arms.

[Slide.]

It can be useful to review briefly hospitalization patterns. As seen in this slide, hospitalizations due to adverse events of all causes were significantly lower in patients on the Alimta arm.

The driving factor behind this rate involved the significantly fewer hospitalizations for the life-threatening complication of febrile neutropenia. Paradoxically, the number of days in hospital was modestly greater in the Alimta arm. This imbalance was due entirely to non-drug-related factors, that is, longer hospitalizations for social considerations and for management of complications of the metastatic lung cancer, not for drug-related issues.

In particular, it is the appropriate concern with the risk of major toxicity that limits the willingness of physicians to advise second-line docetaxel despite demonstrated survival and symptomatic gains from the TAX 317 study as outlined by Dr. Shepherd.

Many individuals involved in new agent investigation have struggled to display clearly this balance between toxicity and benefit, or at least ways of showing the overall effect of major toxicity rates on survival.

[Slide.]

This slide demonstrates one attempt to do this. It is interesting to look at the experiences of all patients on this large Alimta versus docetaxel trial with regard to the time of survival, which was free of serious Grade 4 toxicity.

As is seen in terms of the remaining period of survival, patients randomized to the Alimta arm spent two to three times as long without this degree of serious toxicity when compared with those on docetaxel.

This analysis helps to demonstrate the impact of the more favorable toxicity profile of Alimta when compared with docetaxel.

[Slide.]

We conclude that this large multi-center

trial demonstrated several major advantages for the group randomized to Alimta with the real but limited benefits found in second-line treatment of non-small cell lung cancer. A decrease in the risk of treatment is an important advantage for Alimta.

These significant benefits were found in the key areas of decreased neutropenia and febrile neutropenia, less risk of alopecia and diarrhea, and few drug-related deaths and serious adverse events overall.

From a safety and patient reported outcomes perspective, Alimta is a useful and safe treatment option for patients with non-small cell lung cancer who are candidates for second-line chemotherapy.

The toxicity advantages associated with Alimta with similar symptomatic and quality of life benefits are of great value to patients. The PRO and toxicity evaluations, coupled with the other major endpoints, help to support the finding that Alimta treatment is safer without any compromise in survival response or palliative outcomes.

I would like now to call on Dr. Bunn to summarize these results and to put them into the context of current treatment.

Overall Conclusions

Paul Bunn, M.D.

DR. BUNN: In the past three talks, we have reviewed the relevant data supporting Alimta for the treatment of advanced non-small cell lung cancer after prior chemotherapy. I would like to take a few minutes to summarize the salient issues in your review. I also appreciated Dr. Pazdur's overview of the issues before you and just make a few comments as I go through my presentation.

Of course, you are here to provide your advice to the agency. Your advice is largely going to depend on how much you think about safety and about efficacy, and your confidence in the safety and the efficacy relate to survival, they relate to patient-reported outcomes, and they relate to safety, and we must consider not only the JMEI trial, but what is known in the literature, as Dr. Pazdur alluded to before and how confident are we

about what best supportive care does and how confident are we about what docetaxel does and how many trials are there.

[Slide.]

From this presentation, Alimta clearly provides a new, a safe and clearly an effective treatment option for patients with advanced non-small cell lung cancer in the second-line setting.

This is important as advances in treatment, patients with lung cancer are living longer and they are living better. As a result, more of these patients are candidates for second-line therapy.

At present, they have only one approved option, docetaxel. As noted, docetaxel's use is limited by its significant toxicities and also its use in the first-line setting.

[Slide.]

What about safety? Alimta is clearly safer than docetaxel with respect to any clinically relevant toxicity. Its advantage, of course, is

most marked in the reduction of febrile neutropenia, from 12.6 percent to 1.9 percent.

A secondary benefit that results from this is a concomitant reduction in the use of G and GM-CSF, fewer visits to the clinic for neutropenia, fewer hospitalizations for neutropenia.

However, not all the benefit is isolated to reduction in neutropenia. There was also a significant reduction in Grade 3/4 diarrhea and a reduction in alopecia, a side effect particularly important to patients.

Finally, there was a 3-fold reduction in hospitalization for drug-related adverse events.

[Slide.]

How confident can we be in the safety profile of Alimta? Shown here are the safety results of Alimta in JMEI and in the safety database of all other Phase II monotherapy of Alimta with vitamins.

Of note is the consistent results of Alimta in febrile neutropenia, in diarrhea and alopecia, that were all lower than docetaxel in

JMEI.

[Slide.]

On looking at the direct pivotal trial evidence for survival benefit from JMEI, Alimta has comparable activity with a hazard ratio of 0.99. Median survivals are essentially the same. One-year survival rates were identical and there was internal consistency across all groups.

When indirectly compared to best supportive care, Alimta preserved at least 50 percent of docetaxel's benefit over best supportive care.

With respect to non-inferiority analyses, the 1.11 fixed margin was not met statistically, and many p-values can be calculated different methods, however, we can be confident that Alimta retains docetaxel survival advantage over best supportive care, not only from comparison to TAX 317B, but also comparison to other historical best supportive care trials and the consistency of Alimta's survival result across all first- and second-line trials that you have heard.

[Slide.]

Reviewing all secondary endpoints, the following conclusions can be made from a direct comparison to docetaxel from JMAI.

The time to progression is identical almost. Progression-free survival was the same, and the response rate was very similar. Over 50 percent of all patients on each arm showed improved or stable symptoms.

Indirectly, the response rates of median time to progression for Alimta are consistent across all trials and show relevant activity in all non-small cell lung cancer either in the first line or second line, and these endpoints are superior to historical best supportive care. So, this is what Dr. Pazdur was talking about.

How do clinicians review efficacy of a compound, and how can we tell if one seems similar to another? It is helpful if there are multiple randomized trials.

Fortunately, there are five randomized trials of docetaxel in the second-line setting, and

those five randomized trials are shown here.

[Slide.]

Obviously, a meta-analysis has not been done because some of these are recent, but these are the five randomized trials using docetaxel 75 mg/m2 in one arm. These consistent results with median survivals of 6 to 8 months in all trials give us confidence about the effect of docetaxel.

In each of these five studies, docetaxel 75 mg/m2 was numerically superior to the comparator. Note that two of these trials, the comparator was docetaxel 100 mg/m2 with the worst outcome. That is the reason there are not A versus A + B trials in the second-line setting. Just a little bit of extra neutropenia made survival worst in these patients, and it does limit our ability to develop new agents, because the A + A + B design is very difficult in this setting.

If one were to review, then, the best supportive care results from available second-line randomized trials, once again we see consistent results. Median survival in the best supportive

care arms was 4.5 and 5.5 months.

The BR21 slide results that are shown on this slide is limited to those patients who got second-line therapy, as that trial also included some third-line patients.

These survival rates with the best supportive care are clearly inferior to docetaxel. Finally, when one reviews the median survival for Alimta in this context, the similar outcomes of docetaxel and the superiority to best supportive care is obvious.

[Slide.]

In summary, Alimta merits full approval as a single agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

There are many agents that have received full approval that you know about, sometimes based only on response rate. Here, we have data and efficacy on response rate, progression-free survival, and survival, as well as patient reported outcomes.

Alimta has a superior response rate, progression-free survival, and survival compared to best supportive care. Alimta has similar response rate, progression-free survival, and survival compared to docetaxel.

The safety profile of Alimta is clearly superior to docetaxel. There are many second-line lung cancer patients. They deserve to be offered the safest and most effective treatment that physicians have available.

Approval of this drug will make a safe and effective agent available for patients with this devastating disease.

Thank you for your attention.

DR. BRAWLEY: Thank you, Drs. Bunn, Gralla, Herbst, Shepherd, and Paoletti, and your support staffs for preparing the presentation.

We would now like to move to the FDA presentation, the clinical review and the statistical review.

The clinical review will be given by Dr. Martin Cohen.

FDA Presentation

Clinical Review

Martin H. Cohen, M.D.

DR. COHEN: Good morning. My name is Martin Cohen and I am going to present the FDA clinical review of Alimta, also known as pemetrexed and LY231514.

My review will be followed by the FDA statistical review by Dr. Wang.

[Slide.]

The proposed indication for Alimta is as a single agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

[Slide.]

A single study was submitted comparing treatment with Alimta to treatment with docetaxel. The stratification factors were performance status, disease stage, number of prior regimens, response to the last prior chemotherapy, whether or not the patient received prior platinum or paclitaxel therapy, homocysteine levels, and treatment site.

[Slide.]

I would like to comment on the determination of baseline homocysteine values. Elevated pre-treatment homocysteine values have previously been shown to be an excellent predictor of Alimta treatment toxicity and that reduction of those elevated homocysteine levels with folic acid and vitamin B12 was accompanied by a significant reduction in Alimta toxicity.

Whether vitamin supplementation would also decrease docetaxel toxicity is unknown. There is no reason, however, not to expect a toxicity reduction similar to that observed with Alimta.

[Slide.]

Since docetaxel is the comparator in the Alimta trial, this slide summarizes the clinical materials that were submitted for approval of docetaxel as second-line non-small cell lung treatment.

The first study listed on this slide, as previously discussed, was reported by Dr. Shepherd and colleagues. In this study, patients with

performance status zero to 2, who had failed one or more platinum-based chemotherapy regimens, were initially randomized to receive docetaxel 100 mg/m2 or best supportive care.

Because of early toxic deaths, the protocol was amended to reduce the docetaxel dose to 75 mg/m2. After this amendment, there were 55 patients who received docetaxel 75 mg/m2 and 49 patients who received best supportive care.

Docetaxel treatment gave a response rate of 5.5 percent. The median survival was 7.5 months for docetaxel versus 4.6 months for best supportive care. The difference in overall survival was statistically significant at a p-value of 0.01, and one-year survival was 37 percent versus 12 percent, and that also was statistically significant.

The second study on the slide was reported by Fosella and colleagues. This was a randomized trial comparing docetaxel 100 mg/m2 or docetaxel 75 mg/m2 to a physician's choice of either vinorelbine or ifosfamide.

The study population had a higher percent

of Stage IV patients and more patients who had received two or more prior chemotherapy regimens than did the Shepherd study. The docetaxel 100 mg/m2 dose was again associated with early toxic deaths and will not be discussed further.

The 75 mg/m2 docetaxel-treated patients had a response rate of 5.7 percent versus 0.8 percent for the physician's choice arm. The median survivals were 5.7 to 5.6 months, and the one-year survivals were 30 percent versus 20 percent.

The difference in overall survival between the two treatment groups was not statistically significant. The p-value for the one-year survival difference was 0.025.

[Slide.]

Alimta drug administration is shown on this slide. Alimta 500 mg/m2 was administered intravenously over 10 minutes on day 1 of a 21-day treatment cycle.

Patients receiving Alimta, as mentioned previously, also received folic acid, vitamin B12, and dexamethasone at the doses and schedules listed

on the slide.

Folic acid and vitamin B12 were administered for the purpose of reducing blood homocysteine levels so as to ameliorate Alimta toxicity. Dexamethasone was given to prevent or decrease the occurrence of skin rash.

[Slide.]

Docetaxel drug administration is shown on this slide. Docetaxel 75 mg/m2 was administered intravenously over 60 minutes on day 1 of a 21-day treatment cycle.

Dexamethasone in the doses scheduled listed on the slide was given as prophylaxis against fluid retention and hypersensitivity reactions.

[Slide.]

There were 135 investigational sites in 23 countries that participated in this study, and approximately 21 percent of the study population came from United States institutions.

[Slide.]

This slide demonstrates selected patient

characteristics. As shown the two treatment groups were comparable for performance status, prior chemotherapy regimens, prior platinum and paclitaxel therapy.

Approximately 30 percent of patients in each treatment group had an elevated baseline homocysteine level.

[Slide.]

This slide shows efficacy endpoints. The primary endpoint was overall survival, and the FDA survival analysis will be discussed in the following FDA presentation.

Secondary efficacy endpoints included response rate and duration, time to progression, progression free survival, and lung cancer systems as measured by the Lung Cancer Symptom Scale.

Because progression free survival results mirror time to progression, only the former will be discussed on the subsequent slide. Similarly, because no differences were identified between the two patient groups in any of the Lung Cancer Symptom Scales, symptom burden will also not be

further discussed.

[Slide.]

Alimta treatment resulted in 1 complete response and 23 partial responses, for an overall response rate of 9.1 percent. Docetaxel treatment resulted in no complete responses and 24 partial responses, for a response rate of 8.8 percent.

The overlapping 95 percent confidence limits of the two response rates are listed. Median response durations were 4.6 months for Alimta and 5.3 months for docetaxel.

[Slide.]

This slide shows time to progression for both the intent to treat, or ITT patient population, and the randomized treated, or RT patient population.

As indicated, time to progression was similar for Alimta and for docetaxel treatment groups whether one compares results for either the ITT or RT population groups. For the ITT population, there was a slight advantage of median time to progression favoring Alimta, whereas, for

the RT population, there was a slight advantage favoring docetaxel.

[Slide.]

Now, we get to one of the more controversial aspects of this review, the issue of post-study chemotherapy. The patient population analyzed in this slide is the randomized and treated population.

At the time of disease progression, patients were allowed to receive post-study chemotherapy. This slide lists the drugs that were most frequently used. As indicated on this slide, 126 or 48 percent of Alimta-treated patients and 107 or 39 percent of docetaxel-treated patients received post-study chemotherapy.

Of possible importance to a non-inferiority survival analysis, 85 or 32 percent of Alimta-treated patients crossed over to docetaxel treatment. Patients on the docetaxel arm were not permitted to cross over to Alimta, and they received a variety of other drugs including those listed on this slide.

[Slide.]

This slide shows the median survival of randomized treated populations who received or did not receive post-study chemotherapy.

139 Alimta patients did not receive post-study chemotherapy and 169 docetaxel-treated patients did not receive post-study chemotherapy. The 30 patient difference between the two treatment arms might be important, because patients on both study arms who did not receive post-study chemotherapy had shorter median survivals, 6.2 months for Alimta patients and 5.0 months for docetaxel patients than patients who did receive post-study chemotherapy, as summarized in the last two lines on this slide.

[Slide.]

Because this slide demonstrates that post-study chemotherapy improved survival, it is important to look at patients who did not receive post-study chemotherapy. The presumption might be made that these patients were too sick to receive treatment, and that is why they had a worse

survival.

This does not appear to be the case, however. This slide shows the last recorded performance status of patients who did not receive post-study chemotherapy. Again, there were 139 Alimta-treated patients and 169 docetaxel-treated patients.

As is evident from this slide, the large majority of patients who did not receive post-study chemotherapy were performance status zero or 1 at their last study visit, and conceivably, could have received additional treatment.

[Slide.]

In our previous look at this slide, we were concerned with patient who did not receive post-study chemotherapy. We are now concerned with patients who were treated.

While it appears that all treatments, including post-study docetaxel or post-study other chemotherapy, gave comparable survival results, it must be remembered that these are not randomized patients and that prognostic features of each group

may be very different.

Thus, post-study chemotherapy treatment may well have been of more benefit than post-study docetaxel treatment may well have been more beneficial than other post-study chemotherapy treatment.

[Slide.]

Turning now to safety considerations, this slide shows patient exposure to treatment. The median number of cycles we see by patients on each treatment arm was 4, and there was no striking difference in the percent of planned dose intensity received by patients on either treatment arm.

[Slide.]

This slide summarizes all toxicities experienced by study patients regardless of causality based on their CTC grade. As evidence from this slide, there was no difference between Alimta and docetaxel for Grade 1 and Grade 2 toxicities. For Grade 3 toxicity, Grade 4 toxicity, and Grade 3 or 4 toxicity, Alimta was significantly less toxic than docetaxel.

Alimta's safety advantage for Grade 3 or 4 toxicity comes primarily from less neutropenia, less febrile neutropenia, and less infection accompanying neutropenia.

[Slide.]

Looking specifically at neutropenia, this slide shows Grade 3 to 4 neutropenia accompanied with fever or with infection. Thirty-six or 13 percent of docetaxel-treated patients had febrile neutropenia versus 5 or 2 percent of Alimta-treated patients.

Also, indicated on this slide, documented infection in the setting of neutropenia occurred in 5.8 percent versus zero percent of docetaxel and Alimta-treated patients, respectively.

[Slide.]

Therefore, if one now looks at all toxicities regardless of causality excluding white blood cell events, such as decreased leukocytes and lymphocytes, neutrophils, granulocytes, infections, febrile neutropenia, or other white blood cell related events, there is no longer a significant

difference between Alimta and docetaxel treatment.

For Grade 3 or 4 toxicity, for example, the p-value is 0.781.

[Slide.]

CTC Grade 3 or 4 adverse events regardless of causality are listed on this slide. As indicated, alopecia and diarrhea occurred significantly more often with docetaxel treatment than with Alimta treatment.

Grade 3 to 4 diarrhea occurred at 4 percent of docetaxel-treated patients versus 0.4 percent of Alimta-treated patients.

There was no statistically significant difference in the occurrence of the other listed toxicities - fatigue, nausea, vomiting, stomatitis, pulmonary toxicity, or neurosensory toxicity.

[Slide.]

Turning now to treatment emergent adverse events, of TEAEs, this slide shows all treatment emergent adverse events regardless of causality for which there was a statistically significant difference between treatment groups based on an

uncorrected p-value of less than 0.001.

As shown, nausea, weight loss, increase in hepatic enzymes, the alanine and aspartate amino transferases, and decrease in creatinine clearance were all more frequent in Alimta-treated patients. Alopecia was worse in docetaxel-treated patients.

[Slide.]

This slide shows all treatment emergent adverse events regardless of causality for which there was a statistically significant difference between treatment groups and an uncorrected p less than 0.05 value.

Myalgias, arthralgias, neurotoxicity, and diarrhea were all more common in docetaxel-treated patients, while constipation, fatigue, and skin rash were more common in Alimta-treated patients.

[Slide.]

Hospitalizations present a mixed picture. Docetaxel-treated patients had somewhat more hospital admissions, 364 versus 337, but Alimta-treated patients spent somewhat more time in the hospital, 1,722 days versus 1,410 days for

docetaxel-treated patients.

[Slide.]

As regards efficacy conclusions, you will hear the opinion of the FDA statisticians regarding survival subsequently.

Whatever your views on the relative merits of the survival analyses, however, the fact is that post-study chemotherapy confounds the survival analyses.

With regards to post-study chemotherapy, there are two issues. The first issue is the crossover of 85 Alimta-treated patients to docetaxel treatment. While median survival of these patient is similar to the median survival of patients receiving other chemotherapy regimens, such survival analyses do not take into account possible prognostic differences between the various treatment groups.

The second issue is that patients who did not receive post-study chemotherapy had a shorter survival than those who did receive such treatment. There were 30 more docetaxel-treated patient than

Alimta-treated patients who did not receive post-study chemotherapy.

The large majority of untreated patients had a performance status of zero or 1 at the time of progression, and could conceivably have received additional treatment.

Alimta did show evidence of activity, however, in that it produced a response rate of 9.1 percent.

[Slide.]

The toxicity spectrum of docetaxel clearly differs from that of Alimta, and this slide summarizes the differences between the two drugs.

Docetaxel produces more neutropenia and neutropenic complications, including febrile neutropenia, infections, and need for colony-stimulating factors. It also causes more neurotoxicity, myalgias, alopecia, and diarrhea.

Alimta, on the other hand, produces more thrombocytopenia, more skin rash, more nausea and vomiting, more elevations of hepatic enzymes, a decrease in creatinine clearance, and more weight

loss than does docetaxel treatment.

An important point on this slide is that folic acid and vitamin B12 supplements presumably by reducing elevated homocysteine levels have been shown to ameliorate Alimta toxicity. Whether such supplements, which were not given to docetaxel-treated patients, would ameliorate docetaxel toxicity is not known.

Thank you for your attention.

DR. BRAWLEY: Thank you, Dr. Cohen.

Dr. Yong-Cheng Wang.

Statistical Review

Yong-Cheng Wang, Ph.D.

DR. WANG: Thank you, Dr. Cohen.

Good morning. I am Yong-Cheng Wang, the statistical reviewer for the application being discussed today. In this presentation, I will present the results of efficacy analysis of Study JMEI.

[Slide.]

Here is the outline of my presentation. The results of protocol specified primary endpoint

analyses. Post-hoc 50 percent of retention non-inferiority analyses, which was submitted in the NDA.

The critical issues in Study JMEI. The results of secondary endpoint analyses. Efficacy conclusions will be given at the end of this presentation.

[Slide.]

The protocol specified two study objectives, superiority hypothesis and fixed margin non-inferiority hypothesis.

In the superiority hypothesis, the goal is to demonstrate that Alimta is more effective than docetaxel.

In the fixed margin non-inferiority hypothesis, the goal is to demonstrate that Alimta is not worse than docetaxel by 11 percent clinical benefit, or in other words, that non-inferiority margin is fixed at 1.11.

The fixed margin of 1.11 was specified at the recommendation of EMEA, and was not based on any historical trial data. However, from our

calculation, this margin is close to FDA/CBER technology.

[Slide.]

Here are the results of primary endpoint overall survival analysis for the intent to treat population. For the overall survival, the median survival is 8.3 months for the Alimta group and 7.9 months for docetaxel group.

The study failed to demonstrate superior efficacy of Alimta to docetaxel with a log-rank p-value of 0.93. It also failed to demonstrate non-inferiority based on the fixed margin non-inferiority test. The p-value is 0.256.

Based on the Cox regression model, the HR of Alimta versus docetaxel is 0.99 with 95 percent confidence interval 0.82 to 1.2. The non-inferiority margin 1.11 is less than the upper limit 1.2.

[Slide.]

For the randomized and treated population, the results are similar to ITT population as presented in the previous slide.

[Slide.]

The sponsor also included a post hoc non-inferiority hypothesis of 50 percent of retention of docetaxel effect in the NDA submission.

In this hypothesis, the goal is to demonstrate that at least 50 percent of docetaxel effect will be retained by Alimta. In the current study, we have serious reservation about this analysis as presented in the next few slides.

[Slide.]

There are two major critical issues in Study JMEI. First, the docetaxel effect is estimated from only one small historical trial, therefore, we cannot assure the ability to repeat the results.

Also, we cannot reliably assess the magnitude of the docetaxel effect.

Second, the survival results are confounded by crossover of Alimta to docetaxel.

[Slide.]

I will now go over the details of these

critical issues. The historical trial which is used for the estimation of the docetaxel effect is TAX 317. As presented here, this is a very small trial, total of 104 patients were enrolled with 55 patients in the docetaxel arm and 49 patients in the best supportive care arm.

So, the estimate of the docetaxel effect is not reliable and not robust. Since this is the only one historical trial used for the estimation of docetaxel effect, the constancy assumption that docetaxel effect in Study JMEI is the same as in the historical trail cannot be verified.

It should also be noted that these results are in the ITT population only, and we do not have results based on the randomized and treated population.

[Slide.]

This slide shows the critical issue of treatment crossover of Alimta to docetaxel. There are more than 30 percent patients who crossed over from Alimta group to docetaxel group. Therefore, the survival results are confounded.

[Slide.]

I will now present the results of secondary endpoints analysis.

[Slide.]

This slide shows the results of survival rate analysis. For the 6 month, Alimta has a slightly higher relative risk than docetaxel in the survival rate.

For the 12, 18, and 24 months, Alimta has a slightly lower relative risk than docetaxel for the survival rate.

[Slide.]

This slide shows the results of time to progressive disease. Alimta is not significantly superior to docetaxel for the time to progressive disease in the ITT population.

[Slide.]

This slide shows the results of progression-free survival. These results are similar to the time to progressive disease.

[Slide.]

This slide shows the results of response

rate analysis. Alimta is not significantly superior to docetaxel with respect to tumor response. The results of symptom improvement analysis are not present either, as there was missing data. Results were based on a subset of patients in this open label study.

It should be noted that even though p-values have been presented for all the secondary endpoint analysis, these values are not interpretable, and none of them are adjusted for multiplicity.

Efficacy conclusions. Based on the overall survival analysis, a single, randomized, open-label, multi-center study JMEI in advanced non-small cell lung cancer patients treated with Alimta versus docetaxel failed to demonstrate superior efficacy of Alimta to docetaxel.

It also failed to demonstrate non-inferiority compared to docetaxel.

[Slide.]

The estimate of docetaxel effect based on only one small historical trial is not reliable and

not robust.

In the presence of treatment crossover from Alimta to docetaxel, the survival results are confounded and non-inferiority analysis is very difficult to interpret.

Therefore, the result of 50 percent retention non-inferiority analysis is not interpretable.

Thank you for your attention.

DR. BRAWLEY: Thank you.

As we move forward, I would like to ask Dr. Pazdur if he wants the current questions, Question No. 1 and Question No. 2, and you would like a vote on Question No. 1 and Question No. 2. Thank you very much.

At this point, it is 10:31. I would propose that we go to break until 10:45. I would ask the members to be back in their seats at 10:45. I think we can finish a little earlier today than is currently posted.

[Break.]

DR. BRAWLEY: As we come to order, this is

the section for open public discussion. I understand there is one discussant. I need to say the following:

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee

if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

I am sorry. That is an official sort of thing that has to be read into the record.

MS. POLLACK: I understand.

Open Public Hearing

DR. BRAWLEY: If you can introduce yourself and begin your statement.

MS. POLLACK: Certainly. Good morning. My name is Michelle Pollack and I am the Director of Marketing and Development for the Wellness Community, an international non-profit organization that provides support, education, and hope to people affected by cancer.

For the record, the Wellness Community receives unrestricted educational funding from Eli Lilly, however, we received no funding or compensation for my presence here today.

The Wellness Community offers free

programs including professionally led support groups, educational seminars, nutritional workshops, exercise and mind-body programs, among others.

Our mission is to help people living with cancer regain a sense of control over their lives, feel less isolated, and restore their hope for the future regardless of the stage of their disease.

Last year, we provided support services to more than 30,000 people with cancer including people with locally advanced or metastatic non-small cell lung cancer. Through the virtual Wellness Community on-line, we were able to reach even more people.

At the Wellness Community, we have learned a great deal from those we support and we believe in the importance and value of an educated and empowered patient. Since people with cancer often feel stigmatized, alone, and overwhelmed with grief, they feel stronger and more hopeful when they have more treatment options available to them.

With an estimated 174,000 new diagnoses of

lung cancer in 2004 in the United States alone, with 80 percent of those non-small cell lung cancer, there is no doubt that we are in need of improved treatments, more manageable and tolerable side effects, and greater accessibility to those treatments.

We have the opportunity to expand the chances that these families have for a better life with new treatment options, and we feel very strongly about supporting that opportunity.

Today, I ask you to carefully consider the plight of people with locally advanced or metastatic non-small cell lung cancer and empathize with the range of daily physiological and psychosocial issues that they face.

Please take a leadership role in approving a broader range of treatments and then encourage patients to be informed, empowered, and optimistic about the possibility of longer, healthier lives.

Thank you.

DR. BRAWLEY: Thank you, Ms. Pollack.

I believe there is no other speakers for

the open public hearing, am I correct? Hearing none, then, we are going to move on.

I would like to ask the committee to address any questions to either the sponsor or the FDA.

Dr. D'Agostino.

Questions from the Committee

DR. D'AGOSTINO: If I read correctly the way the FDA has put the questions to us, the discussion really gets onto secondary events and toxicity, and so forth, but there is a couple of comments in the front statement of the FDA about the ability with the one small historical study to actually estimate survival and also the crossovers.

I know they were mentioned in the discussion of the sponsor, but I think it would be useful to hear a response from Lilly in terms of those two questions, so that we discuss them and put them aside, or discuss them and think they are important.

DR. PAOLETTI: No crossover is inevitable in a situation like that especially in the United

States. I will ask Dr. Frances Shepherd to review the historical context of third-line treatment in lung cancer to answer the question in this way. Then, I will ask Dr. Bunn to respond to the question in terms of what we have observed in our data, and, finally, Dr. Scott Emerson from a statistical point of view to address this issue.

DR. SHEPHERD: Yes, we really do not feel that there was a significant effect on survival from crossover. If we could have the first slide projected, please.

You may be uncomfortable with the survival that was achieved with docetaxel in the TAX 317 or the TAX 320 trials. There have been several studies that have followed after that of docetaxel 75 mg/m2, and as Dr. Bunn showed you, every single one of those studies had a median survival in a very tight range that was similar to the TAX 317 trial.

So, we now have at least five randomized trials of docetaxel showing where the median survival is expected to be in this clinical

scenario.

With respect to the best supportive care arm, we have fewer studies, and there has been no study in the third-line setting of chemotherapy.

Looking at this slide, though, a retrospective study was done by the M.D. Anderson and Institute Gustaf Ruce [ph] looking at 700 patients who had had first-line and second-line chemotherapy. Of those, 43 were treated with third-line.

The response rate was a mere 2.3 percent, and the median survival was less than four months. When you look on the other side of the slide, this is the subset analysis from the TAX 317 study. This is the only randomized data that exist that compare third-line chemotherapy to best supportive care. We do not underestimate the small sample size here. These are exploratory analyses, but there is nothing in this curve that would suggest that third-line chemotherapy contributes to survival.

Next slide, please.

I am going to show you the survival curve from the BR21 trial, No. 568. This is the survival curve in the BR21 trial, which was a trial of placebo and best supportive care versus erlotinib in the second- and third-line setting. Erlotinib showed a significant survival advantage.

I show this to you for two reasons. One, to show you that the survival of the untreated group, the median survival was 4.5 months, almost identical to the best supportive care group of the TAX 317 trial.

So, we have a supporting trial that provides a similar survival advantage or disadvantage with no treatment. So, it gives us a little bit more confidence that the best supportive care group in TAX 317 was exactly what we would expect to see in larger populations.

Now, in actual fact, if you look carefully, more patients on the docetaxel arm received Iressa, a drug very similar to Tarceva, in the third-line setting. So, in actual fact, the only treatment that has been shown to prolong

survival in the third-line setting is an EGFR inhibitor and more patients on the docetaxel arm, four times as many patients on the docetaxel arm actually received that kind of treatment.

So, if anything, that would have favored docetaxel and not Alimta.

DR. BUNN: Not only do we wish that we had more treatments in the third-line setting to make people live longer, but when we look at the analysis, it is not, I don't think, appropriate to say that the third-line treatment made people live longer in the study.

People who got chemotherapy in the third-line did live longer, but that is just a prognostic group. That is like saying responders live longer than aggressive disease. That doesn't mean that the treatment made them live longer.

But we looked very hard to try to sort out whether there was any evidence that third-line treatment did anything here to the best of our ability.

So, you see here on the top of this curve

is the overall survival results, and presumably, the third-line therapy is given after some period of time, and if it had an effect, the curves might look different at the end.

I think it is easy to say, in the survival curve, there is no difference in the beginning, there is also no difference at the end.

If there had been a difference in progression, the time of progression, it might have favored one group, and on the lower left you see that the time to progressive disease was identical in the two things.

Finally, if there was an effect post study, the post-study survival is shown in the lower right curve, as I showed before, and there was absolutely no evidence, not even a hint that there was some survival effect in the post-study groups.

Obviously, post hoc analyses like this are difficult, and there are many statistical issues. I am going to ask the statistician to get up, from a clinical point, no matter how we looked at this,

we couldn't find any evidence that there was an effect of post-study treatment that was different between the groups.

DR. PAOLETTI: Dr. Emerson, please.

DR. EMERSON: Scott Emerson from the University of Washington. Slide 64, please. This is a slide, that this is now the fourth time we have seen this in some version, and as Dr. Bunn remarked earlier, this is a very biased presentation, this is not really a very informative presentation at all, and I would just like to point out what we can say from this and what we can't say from this.

We certainly can say that those people who survived long enough to get post-study chemo, survived longer than those who didn't survive longer to get post-study chemo.

The grouping is true, that there is longer survival among those who got post-study chemo, but that is not quite as strong as what Dr. Cohen said when he said that the post-study chemo made you live longer.

So, to address that, if I could have the slide 669. We did an analysis that tried to compare apples more with apples. Let's compare those people who got post-study chemotherapy at a certain point in time with other people who had also survived that long, so we will assign your group as to whether you got post-study chemo according to the time that you are on the study.

So, this time-variant covariate analysis allows us to compare Alimta to docetaxel, keeping that post-study chemo variable constant across the groups being compare.

It also allows us to estimate the effect of post-study chemotherapy. Let me qualify what that effect is. It allows me to estimate the difference in survival among those who got post-study chemotherapy to the survival among those who didn't.

I am not going to claim that this is truly a cause and effect, because, of course, this isn't randomized. There was a lot of physician discretion that went into this.

But from this analysis, if I look among patients who had no post-study chemotherapy at any time during the study--and again I would have switched them to another group if they had--the Alimta to docetaxel hazard ratio is actually 0.84, it is looking a stronger effect than we saw when we just did the intention to treat or RT analyses.

If we look at the effect of post-study chemotherapy, now I am just going to look at among those patients alive at any given time, on the docetaxel arm, who are getting post-study chemotherapy compared to those on the docetaxel arm that aren't getting post-study chemotherapy at that same time, the hazard ratio is 1.12. This estimate suggests there is a 12 percent increased risk of death if you get post-study chemotherapy.

On the Alimta arm, it is far more striking. There is a 58 percent higher chance of death among those subjects on the Alimta arm who are getting post-study chemotherapy relative to those who don't.

So, this nonrandomized comparison, which I

don't really believe is the effect of post-study chemotherapy, but this analysis would suggest quite the contrary to what was worried about, was that the post-study chemotherapy is responsible for the better survival is actually if we took this at face value, you would say if we could just write in the indication that you don't do any post-study chemotherapy, we are doing better than docetaxel.

I don't believe that, because I truly believe that physicians are pretty smart.

Can we go back to slide 64 for a moment.

What we see here is that 139 subjects had no post-study chemotherapy on Alimta and 169 subjects on docetaxel. My personal belief would be that physicians, faced with a progression or a patient who is failing on Alimta, would recognize that docetaxel has been approved for second-line therapy and those patients should really give that chance.

I think that physicians are pretty able to recognize when patients are in trouble, that they are on a path towards worse and worse conditions,

and I personally believe that that is the primary effect that we are seeing with that greater rate.

Patients on docetaxel could not be switched to another therapy if, in fact, they were already experiencing a fair amount of toxicity. You wouldn't want to try them again on that chemotherapy. We may just be seeing physician behavior, so again, I am not claiming that that higher post-study therapy is there, but I am claiming that we don't have any evidence to suggest in this data that there is an added benefit of post-study chemotherapy to improve survival.

Lastly, if I could see slide 20, just to make a point again that Dr. Shepherd made, and that is this concept that in this study, the patients receiving that third-line chemotherapy were not randomized, but in TAX 317, they were randomized.

It is a subgroup analysis, but when we did a randomization based on that, we clearly saw no benefit. That would be presumption, that if we had done randomization to third-line therapy, that this would likely have been the case and that we

wouldn't have seen that added risk.

DR. PAOLETTI: Dr. D'Agostino, should we answer your second question, or do you want to continue on this issue?

DR. D'AGOSTINO: It is up to the Chair.

DR. BRAWLEY: Go ahead with the second question.

DR. D'AGOSTINO: You don't want to ask questions on what they just presented?

DR. BRAWLEY: Does anyone have questions on what was just presented?

DR. D'AGOSTINO: I have a question.

DR. BRAWLEY: Oh, go ahead, I am sorry. I misunderstood you.

DR. D'AGOSTINO: What if Alimta was not effective at all, and it was just the post-chemotherapy of the crossover that gave these individuals an increased survival? I don't think there is an interpretation that they just gave us, but there is another interpretation that is just as viable, that the crossover is adding quite a bit to the--it's not the third line--it's the second-line

treatment.

The other thing is that I am concerned with really Dr. Cohen's presentation where he showed that those who didn't get the added chemotherapy on the prognosis basis looked pretty good, and it is hard for to me to understand that the third line isn't helpful, yet, the ones who didn't get any added to their line, that some are crossovers, some aren't doing as well.

I don't really want to make a big statistic discussion out of it, because I agree 100 percent that we are beyond statistics, it is just that it does raise a question about how to deal with this type of data.

DR. EMERSON: Could I address your second question just slightly. Performance status, we got identical results essentially in the time variant covariate, if I adjusted for a time variant performance status, as well, in this trial.

DR. PAOLETTI: As regards the question about efficacy, it's a point like progression-free survival, time to progression of disease where

there is no effect of crossover, the results are identical, as well as response rate.

Dr. Bunn.

DR. BUNN: I think if Alimta had no effect in the early analysis for time to progression, we would have seen a difference, and we would have seen a survival difference if it didn't have any effect. We probably would have seen a response rate different, and we probably would have seen a patient reported outcome difference if it didn't have any effect.

DR. D'AGOSTINO: I mean that was an extreme statement I made. The point is that it may be it is not as effective as, and it is the added boost of the chemotherapy, the second- or the third-line chemotherapy that makes the difference. I don't see how you can sort that out from the data.

DR. BUNN: I would just like to comment about, you know, giving third-line therapy. You know, we are oncologists and we generally like to offer therapy where it might be effective, and I

think that most of our patients would prefer to get treatment where it would be effective.

There does come a time when neither the patient nor the physician is anxious to give chemotherapy. Usually, that is in people who are quite ill. Sometimes they are ill and show up as a performance status, but sometimes they have been beat up by chemotherapy and they don't have sufficient blood counts, or they have neuropathy, or they have many other things that would preclude.

It is hard to imagine, to me, that the physicians would have a bias in the third-line setting about treating or not treating patients. As a doctor, I find that hard to believe.

DR. D'AGOSTINO: I didn't say anything about bias.

DR. PAOLETTI: Dr. Shepherd.

DR. SHEPHERD: Just one further point. I think the point that Dr. Cohen made showing us how many good performance status patients do not get chemotherapy underlines the belief of the lung cancer treating oncologist that third-line

chemotherapy is not beneficial.

When you have no evidence from historical data to suggest a survival benefit, when you have a response rate less than 3 percent, the potential for toxicity is higher than the potential for benefit, so clinical practice on the whole is not to offer chemotherapy.

You don't want to make a performance status zero or 1 patient, performance status 3 or 4 with toxicity, if you don't have a good chance of benefit.

DR. NGUYEN: Maybe another clarification on this point. Binh Nguyen, Eli Lilly, Oncology Platform Team.

I would like to address Dr. D'Agostino's questions. 471, please. Out of those performance status that were shown by Dr. Cohen, actually, the patient who would perform zero and 1 and alive at one month after discontinuation is only half, so not all those 139, 169 could receive chemotherapy, so you have to take that into consideration and look at the difference between the two arms. A

drop now is not 30 patients, it is only 12 patients.

So, it is obvious these patients actually die very quickly, that is why they couldn't receive post-chemotherapy even thought they had a performance status of zero and 1. I think these data are very important.

DR. D'AGOSTINO: I think this is the type of discussion I was hoping to hear in terms of responses, why are they looking so good, are they really dying or not dying. The group actually again, even though there is this discussion that we heard, the ones who did not get the second shot out at the third-line chemotherapy do not do as well, and it is just not clear to me yet that there is an obvious reason that one can see on that.

DR. BRAWLEY: Dr. D'Agostino, did you have a second question?

DR. D'AGOSTINO: I asked a second question. That was about the sample size.

DR. BRAWLEY: Dr. Mortimer.

DR. PAOLETTI: Actually, you were

referring to the non-inferiority design, et cetera. Again, we acknowledge that the historical data at the beginning, when we designed this trial, were limited to the TAX 317.

However, as Dr. Bunn was showing at the conclusion of his presentation, additional historical data, additional data were growing during all this year, and most importantly, the results from our trial in 288 patients are confirming the performance of the TAX 317.

I would like to ask Dr. Don Berry to answer the question from a statistical point of view.

DR. BRAWLEY: I think we need to move on.

DR. MORTIMER: I have two sort of questions. One relates to a comment Dr. Shepherd just made. I mean is it possible to ferret out the patients who were on the docetaxel arm who might have actually refused therapy because of the risk of hospitalization since they were hospitalized more often.

Secondly, is there a difference in

patterns of relapse in these arms, specifically, brain metastases?

DR. PAOLETTI: Not to my knowledge, but I will ask--no, actually.

DR. BRAWLEY: Dr. Perry.

DR. PERRY: Thank you. I have a question for Dr. Pazdur. Did the study proponents run this proposal through the FDA, was it approved by the FDA before it was actually set into place?

DR. PAZDUR: I would have to check if it had a special protocol assessment. Obviously, it was discussed with the sponsor, the design of the trial. Whether or not there was a special protocol assessment, I would have to check on that.

DR. PERRY: The issue to me is there is a lot of criticism of the protocol design, particularly about the crossover, and if the sponsor got approval from the FDA first, I think it is a little unfair to come around post hoc and say, well, you didn't allow for the crossover, which I don't think is valid in the first place, but I would like from my own point of view whether the

FDA really approved this.

DR. TEMPLE: Can I just comment a little. Nobody is criticizing the crossover, it is completely unavoidable when the other drug is available. The only question is what impact it has on the somewhat marginal equivalence studies, that's all.

The point was I think this should be emphasized, if there is even a modest effect, one that you would have difficulty detecting in a clinical trial in that setting, it could have an effect on the equivalence margin. That is really the main point of what Dr. Cohen was saying.

I don't think we have reason to dispute any of the analyses that were done. You can't prove there is an effect. That would be very difficult because the effect at best is small, but taken in the context of the whole non-inferiority design, there could be questions about whether that undermines it some. I think that is the point. But it is not that anybody did the wrong thing or that we think they did.

DR. SRIDHARA: This is Rajeshwari Sridhara. I am the Team Leader for Statistics. Regarding your question regarding protocol design, et cetera, our understanding was that they would do a superiority and fixed margin analysis, and, yes, we knew that there would be crossover, but in superiority trials, this is not an issue.

When it is non-inferiority and when they are crossing over to the same control as they are testing, the question arises are we comparing control to control or are we comparing treatment to control. That is the importance of crossover that we are talking here.

DR. PAOLETTI: Just for clarity, we did have a special protocol assessment.

DR. PERRY: Thank you. I have another question, Dr. Brawley, if I am permitted.

This is for Dr. Cohen. You made a comment that the B12 folate supplementation might have had an effect if it were given to the people on the docetaxel trial.

Is there any evidence anywhere in medical

oncology that vitamin B12 folate supplementation decreases toxicity in any group of compounds other than the folates?

DR. COHEN: Well, this was pretreatment elevation of homocysteine, so it had nothing to do with giving an antifolate. This was baseline. But to answer your question, no, there is no evidence that this effect would be seen with other drugs, but there is no reason to exclude that possibility either.

DR. PERRY: Well, yes, I think there is every reason to exclude it. I mean it hasn't been done, but I mean you could say that these people didn't get yogurt either, and that didn't have an effect. I think that is really an invalid point to bring up.

It is the antifolates that have the vitamin B12 supplementation effect, not the taxanes, not the alkylating agents, not any other class of drugs.

DR. COHEN: I guess we disagree.

DR. PERRY: I would be happy if you could

show me any evidence anywhere in the medical literature that supplementation with vitamin B12 and folate affected the toxicity profile of any group of drugs.

DR. COHEN: I wasn't involved with this study at the end of Phase II meetings, it was another medical officer, but it is my belief that the sponsor was asked to give vitamin supplementation to the docetaxel group also, and they chose not to.

DR. PERRY: I can understand that because there is no evidence that it works.

DR. TEMPLE: For what it is worth, in the mesothelioma--correct me if this is wrong--but we believe that in the mesothelioma trial of the same drug, it was given to both groups. Is that not correct?

DR. PAOLETTI: Yes, it was given to the both groups, but the trial was a single arm, randomized trial, so when we have to modify the protocol--single, blind, sorry--randomized trial, and you have to amend the protocol to reduce

toxicity, we were obliged to give the drug.

DR. TEMPLE: So, it was just for blinding.

DR. PAOLETTI: For blinding, correct.

DR. TEMPLE: There is a certain advantage when you don't have information to exercise the caution of giving it to both groups, but we don't think there is evidence that it would help the--

DR. PAOLETTI: I just would like to remind you that the patients were stratified by nutritional status as measured by homocysteine, so at least the nutritional status would balance, and we did look also about the toxicity by homocysteine levels, and there was no difference in the docetaxel arm.

DR. BRAWLEY: Dr. Levine.

DR. LEVINE: I would agree with Mike related to the B12 and folic acid. It doesn't really make sense to me that it would have any ability to ameliorate the toxicity on the docetaxel arm.

My question relates to some of the toxicity issues in terms of hospitalization. I

think the data is quite compelling related to the increased risk of neutropenia and febrile neutropenia and infection with the docetaxel arm. What I don't understand is the hospitalization. The numbers of hospitalizations were also decreased with the study drug, but not the number of days.

My question relates to why. I subtracted the social days and I subtracted the protocol treatment days, but even then it is a little bit higher on the study drug, it is 1,199 versus 1,147.

Do you have days in U.S. patients or what explains that?

DR. PAOLETTI: Dr. Gralla will answer to your question.

DR. GRALLA: I think I had the same issue and wanted to look at the data and it is kind of confusing, but let me just go through with you how I looked at it, and I looked at it exactly the same way you suggested, and Dr. Cohen also looked at the patients treated in U.S. and Canada, North America, the 21 percent versus the other three continents.

What you find is if you look at those 21

percent treated in the U.S. and Canada, where you don't have those confounding issues of social admissions and protocol admissions, that what you have is a higher number of patients admitted for drug-related reasons for docetaxel, and what you have is the same number of patients admitted in North America for non-drug related issues, exactly what you would expect, that because of the febrile neutropenia, you would expect to see more patients admitted with docetaxel for drug-related reasons, but you would expect to see the same for non-drug.

Then, you go to the other three continents and what you see in the other three continents is again for drug-related issues, you find fewer admissions on Alimta, but for non-drug related issues, there is an imbalance.

This relates to about 4 percent of all the patients on the protocol all together, and what you have are more patients admitted for disease progression reasons, for complications, so these are for cord compression, limb pain, pleural effusion, COPD reasons, and for whatever reasons

that are not clear, and there is no evidence that it is due to drug toxicity, you have longer hospital stays, and some of these hospital stays are 30 to 60 days, and you find three to four weeks for pleural effusion drainage.

So, for whatever reason, and some of the countries lack hospice, there is this imbalance, but it is not in drug related issues, it's in these non-drug related areas, and I think again, the 4 percent of patients that amount to all this excess, that this is just a fluke bad luck result, because there is no other explanation that I can find, spending a good amount of time looking at these data.

DR. BRAWLEY: Ms. Ross.

MS. ROSS: Thank you. First of all, I would like to thank Mike for bringing up the clarification about the B12 effects on antifolates. I really had to do something else from your remark, Dr. Cohen, and I am glad it was clarified.

I want to ask two questions, two questions that will help me understand better as a patient

advocate what FDA is really saying, if you will bear with me.

FDA is taking the position that the sponsor has not proven non-inferiority. Is FDA then taking the position that the drug is inferior, that Alimta is inferior?

DR. PAZDUR: No, basically, what we are looking for in a non-inferiority design is an effect on survival. One could win on survival either by an improvement in survival or non-inferiority.

What we are saying here is because of our concerns of crossover because of the lack of a really good historical database, the analysis of non-inferiority may be in question. We are not saying that it is an inferior drug. We are saying basically that we have concerns that an effect on survival may not have been convincingly demonstrated, and for regular approval of a drug, one has to have confidence of an effect on a clinically meaningful endpoint, such as survival. That is the issue.

MS. ROSS: Thank you for that clarification.

DR. TEMPLE: Can I just take half a minute to describe the non-inferiority problem?

[Laughter.]

DR. TEMPLE: Okay, maybe two minutes.

In situations where you cannot treat people, your only choice is to be better than the standard therapy or to show that you are not worse by more than certain amounts. So, we call these non-inferiority studies, but that is a misnomer. They are really not too much inferiority studies, and not too much means you have preserved a reasonable fraction of the known effect of the control agent. That is what you do.

The simplest way, and the last one that I must say I have been able to understand fully, because statistics takes over after that, is this. You make an estimate of what your effect is of the control from the historical experience.

So, we have that study. It is a small study and it clearly showed an effect of docetaxel,

but because it was small, the confidence interval was wide and the 95 percent confidence interval for how much better was that it was only 12 percent better than the control.

So, one way of estimating the absolutely known effect of the control agent is it has 12 percent on survival. For reasons I will explain, people consider that too conservative, but let me start there.

If that is what you believe, then, you want your comparison of the new drug with the control drug to rule out a difference of more than 12 percent, because if it was more than 12 percent, then, there would be no effect of the new drug at all. In fact, given that we are talking about lethal disease, we often ask that some fraction of that effect be preserved.

So, if you thought the effect of the control is 12 percent, you might ask that you rule out a difference of more than 6 percent, and if you did that, then, you would say you have shown non-inferiority. That is what it means.

Now, the trouble with that is that if you take the worst case for the control agent, that is, that the effect is only 12 percent, when the point estimate of the effect was more like 40 percent, that is a very conservative choice, and it makes it very difficult.

Ruling out a difference of 6 percent or even 12 percent is a very hard thing to do. You would need a study that is very, very large. So, a lot of people have been working on more conservative--or less conservative, if you like, less conservative ways to do these studies, and they are statistically complicated, but at least one of them, and the one that was used by Lilly, involves--sorry, I have one other thing to tell you.

We also calculate that when you use this 12 percent value or something like that, you have got a study that gives you an equivalent of a p of 0.003, which is more than we usually demand. So, people have thought about how we could come up with an analysis that is closer to what we usually want,

you know, a p of 0.05.

One method of doing that was developed by Mark Rothmann who works here, and that is what Lilly used. Basically, he calculates an interval that is different from the 95 percent confidence interval, that, if used, will preserve a p-value of something roughly equivalent to 0.05.

I understand from a conversation at the break that when Lilly did that, they used something like a 65 percent confidence interval. Now, if you do that, instead of having a 12 percent effect of the drug, you have something larger. I am just making it up, but say it is 25 percent effect or 30 percent, I don't know, I didn't get that number although I gather it has been submitted to us.

When you do that, ruling out a difference of 30 percent in this study, you can see the study did rule out a difference of 30 percent because the upper bound of the worseness was I think 18 percent or 20 percent.

So, depending on what you think and what you are willing to say the effect of the control

agent is, you succeed or fail in your non-inferiority study. The difficulty is there is not a lot of agreement, it is very complicated. Most clinicians can't understand what is going on, they depend entirely on the mathematics of it, which is always a problem for me, I like to understand.

But anyway, that is what we are talking about, and that is what all these discussions of methods have been about. The 11 percent that they tried to do and failed sort of corresponds to that initial 95 percent confidence interval lower bound, and that is highly conservative, and they didn't win on that, but they may have won--that is what the debate is about--on a less conservative attempt to show that you have preserved a reasonable fraction of the effect of the control agent.

I don't know if that helps or not.

MS. ROSS: Could I beg your indulgence and ask one other question on that point?

DR. TEMPLE: Yes, but you have got to give me another 30 seconds.

MS. ROSS: Thank goodness Dr. Fleming is not here.

[Laughter.]

DR. TEMPLE: He would have said the same thing I said.

MS. ROSS: Suppose we turn the tables. Suppose Alimta were the already approved drug for second-line treatment for non-small cell lung cancer, and it was docetaxel that was here seeking approval.

Based on the numbers that you have seen, would docetaxel have been able to demonstrate non-inferiority to your satisfaction?

DR. TEMPLE: Well, you have to tell me how big the effect of Alimta was, so I can create an appropriate non-inferiority margin given the new equivalence of the measured results here, you might that if you knew the Alimta effect size very well, this might have been successful, but a lot depends on how well you know the control drug effect.

In this case, you had quite a dramatic effect in the small study, meaning that the

confidence interval is rather large even though the effect was very impressive in that small study.

So, if Alimta had a big 250-patient study, a 40 percent reduction, and the confidence interval was very narrow, a study like this might persuasively show equivalence or non-inferiority.

MS. ROSS: For docetaxel.

DR. TEMPLE: Yes. I should say one other thing. We recognize this is a huge problem because calculating--first of all, you want drugs that might be a little safer, and at the same time, you want to be sure that they still have the desired effect.

I know everybody looks at those Kaplan-Meier curves and they look at them and they say how could there be any difference. The trouble is the effects on the Kaplan-Meier curve of the drugs that are effective are very modest, and there could be a difference or, you know, that is what is being debated, and you wouldn't want that difference, you wouldn't want to lose the effect even if it's small, but it poses a tremendous

problem for manufacturers who want to show non-inferiority. It is very hard.

DR. BRAWLEY: Ms. Ross, we have the additional problem, you know, we just heard a wonderful statistics lecture, and thank you for giving us the lecture without confusing us, but you can have a situation where--let me just as a simple country doctor sort of thing.

You can have a drug that has a 20 percent response rate in a disease, but has terrible toxicities, and there are certain patients who might look at those toxicities and say, hey, I will take a drug that has a 15 percent response rate with a lot less toxicity.

The problem we have is where do we go from there, because that might actually be what we have been presented with here. I made up the numbers, they are not applicable to this issue.

MS. ROSS: But I think your point is exactly what we are looking at here. We have two drugs very similar in effect. Whether the hair splitting on proof of non-inferiority goes one side

or the other, the difference is in toxicity.

As has been pointed out several times, there is only one drug approved right now for second-line chemotherapy for non-small cell lung cancer, and if that is going to make a difference in infection and neutropenia and in hair loss, I mean this is a very big deal. You all kind of glossed over the hair loss thing, but you have a patient who is very sick with lung cancer, not losing their hair makes a big difference in their attitude and general feeling of wellness.

DR. TEMPLE: But presumably, you would still want to be sure that it had the effect you were using it for, you wouldn't want to lose it all.

MS. ROSS: Well, according to all the charts I saw, it is very similar.

DR. TEMPLE: Well, that is the point, that is necessary.

MS. ROSS: It is very similar, but it has less toxicity. Well, certainly I would go for that drug, and I hope my doctor would, too.

DR. TEMPLE: Right, as long as you are reasonably sure that it has that effect. That is what we would all say.

MS. ROSS: Reasonably sure that it has an effect.

DR. TEMPLE: The desired effect on the tumor and on survival.

MS. ROSS: Someday we are going to be sitting around this table talking about drugs that increase survival by two or three years. We are not there yet.

DR. TEMPLE: No, we are not.

MS. ROSS: We are only talking about months in any event, and if you have a drug that gives you less side effects and does the same thing, I think that the lung cancer patients deserve that option, and I would argue for full approval for this drug. It is not fair they only have one now. This is a horrible disease.

DR. BRAWLEY: We will get to the questions in a little bit.

Dr. D'Agostino, I know you wanted to ask a

question, but I think Dr. Paoletti and his group have a rebuttal to the previous question.

DR. PAOLETTI: Yes, if we may have our additional 30 seconds to discuss about the issue, and I will give to Dr. Berry and then Dr. Bunn to comment on that.

DR. BERRY: Donald Berry from M.D. Anderson.

This is related to Dr. Temple's discussion and also to Dr. D'Agostino' second question. If I could have slide 450, please.

This shows better, I think, the confidence interval that we have been discussing that goes from 0.82 to 1.20, and it puts in perspective the fact that Ms. Joss was just talking about, it looks similar. The similarity has much greater likelihood than the N's of the confidence interval. We are talking about a ratio of 5 or so here in terms of degree of likelihood, so it is much more likely that the survival is the same in both than that you are the N's of those intervals.

451, please. this shows the confidence

interval, actually, the 90 percent confidence interval for the hazard ratio for the comparison docetaxel to best supportive care. The 95 percent confidence interval goes down to 0.35 and up to 0.88. The 0.88 is the 12 percent or the 1 minus 12 percent that Dr. Temple mentioned.

Again, this confidence interval is a good deal wider although it looks the same from the previous picture, and that reflects the fact that this study was about one-fifth the size of the previous study.

Slide 565, please. The concern about only one small historical study concerns me as to how we are going to do this. I mean I agree with Dr. Temple that we are not there yet in terms of understanding everything about non-inferiority trials, but what this means is that there is only one trial comparing best supportive care to docetaxel, and there won't be any more.

That means that to show a benefit, we would have to have enormous trials. If we had many large trials, an infinite number of patients, we

would still not be able to show, on the basis of the comparison with the historical data, that the drug is equivalent to a preserves a benefit that docetaxel has even--and this gets to Ms. Ross's point--even docetaxel itself couldn't be shown to be non-inferiority to itself.

The precision of the trial, the previous trial, is, of course, not very great. The number of patients, as pointed out by everyone, is 104. There is great imprecision, and that limits any comparison, but the Rothmann analysis and other reasonable analyses account for that imprecision. Even though the study is small, it is possible to make the comparison.

What are we left with in terms of showing non-inferiority? The FDA is taking away historical study comparisons, and that means we would have to show a comparison--the "we" being the medical community--would have to show a comparison with docetaxel itself, which would mean thousands or 4 or 5,000 patient trials, and that is not in the best interest of patients.

DR. PAOLETTI: Dr. Bunn.

DR. BUNN: Some people aren't going to believe this, but I actually have empathy for Dr. Pazdur and Dr. Temple. I think that they are trying to do the best things, as well. They also have regulatory issues, and one of their regulatory issues is there has to be adequate and well-controlled trials.

Many times in the past, historical controls serve as adequate and well-controlled trials, many, many precedents for that, and one of the issues is not only how comfortable are you with this one trial, okay, but do you have any historical data that gives you confidence, as well. Oftentimes, you know, Gleevec, you have a response rate, when you are expecting none, you get 60, you know, that is an adequate and well-controlled trial.

If we could have slide 560, the slide says that docetaxel evidence, you know, we have a number of historical studies that not only discuss survival, but also discuss response rates and

progression-free survival, as well as patient reported outcomes.

There are patients who get placebo or best supportive care who have objective responses, and that is, of course, their pneumonia getting better, and we can quantify that because there have been randomized trials against best supportive care, and they all show a response rate of 1 percent or less, indicating that 1 percent of the time or less, you have a pneumonia that gets better with antibiotics, and you think that the drug did something.

But we have lots of trials to show that both Alimta and docetaxel cause response, and we can compare that to best supportive care. We also know from the randomized trials that the median time to progression is very short with best supportive care, and we can be relatively confident that that interval is much longer in patients who get some therapy that has an effect.

I am not the best supportive care guy, but there are backup slides, I don't think we need them, to show the same for patient reported

outcomes. I personally believe that another way to look at this is are we confident that there is an effect of the drug from historical trials, not just TAX 317B.

DR. BRAWLEY: Thank you.

Dr. D'Agostino.

DR. D'AGOSTINO: The comments I wanted to make and the question fits in very well with this.

I think that no matter how you look at the studies, at a study that was presented, there is this problem of the crossover and what does it lead to. We don't know how, we are going back and forth, but we really don't know how to handle it, and it is there, and it is not a criticism of the design, it is a fact of reality.

The comment about the non-inferiority and the problem there is that we don't, as a committee, want to set a precedent, that we somehow or other feel that one small study will do the job, and the concern that the FDA has, if I understand it correctly, is that one small study has a lot of variability, and they are still not convinced that

maybe we have adjusted enough for it, and maybe the statistical analysis for the straight-out approval is questionable.

But I thought I heard at the beginning of the presentation that was made by the FDA, that this was under the accelerated approval type of mode, and the accelerated approval type of mode takes us to a different level of sort of approval process.

Could you go over that?

DR. PAZDUR: First of all, there are several issues that I want to address here because I think when we brought--our purpose in bringing this application, it really reflects a lot of the problems that we have been having with non-inferiority analysis.

By no means do I want anybody to walk away with the feeling that we are saying that this drug is inactive. I think we feel very comfortable in some of the surrogate endpoints, response rates. I made the statement that we have accepted similar response rates for accelerated approval, to take a

careful look. It is not just adding up the numbers of toxicity, it is really clinically getting down and seeing what are the real advantages of this drug.

But accelerated approval, because we do have this issue, are we dealing with a true effect on survival, do we want a regular approval of this drug, and have we adequately demonstrated that effect.

If we really haven't, then, obviously, that produces precedents which we may not want to get into. We do have accelerated approval that will allow us, number one, if the drug has an advantage over available therapy and toxicity, could be that, and has a demonstrated effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, such as response rate, that we could move for approval in that situation.

So, that was the avenue that we were taking because of the concern that we had for what is the effect, has this been clearly demonstrated on survival. But I think there are big issues here

that this application brings forward for the whole area of oncology and how to develop drugs in this non-inferiority aspect.

Many other therapeutic areas can use placebo-controlled trials. In oncology, that is tremendously difficult to do, hence, we are stuck either with superiority trials A versus B, where you have to show not only the benefit of your drug, incremental benefit, but the entire effect of the other drug to win, or you could do an add-on trial to demonstrate an incremental benefit, but then you have to have a situation where you could combine the two drugs together.

The other area is we have an issue of crossover, and that is going to be with us. You know, we totally realize that if there is a commercial drug out there that you are comparing it to, a large number of people are going to be getting that drug at the time of disease crossover, and that does pose a problem to looking at non-inferiority analysis.

The issues of what constitutes an adequate

database is very difficult. If you look at our previous non-inferiority approval that we did on non-inferiority, and with capecitabine several years ago, we had approximately 10 studies which isolated the effect of 5FU-leucovorin versus 5FU. That luxury of having multiple trials was done because there wasn't any drug activity or meaningful drug activity for almost three decades in metastatic colon carcinoma.

We aren't going to have that again, and thank God, because that obviously is not identifying active drugs, so these are essential problems that we are going to have to face with non-inferiority, and that is why we brought this application to bear.

How do we handle this if we can't really determine a true treatment effect to preserve, how do we address the issue of crossover, and the accelerated approval program does give us the option of dealing with this problem from a regulatory framework if the drug really has a meaningful reason to be approved here, i.e., a

toxicity reduction.

DR. TEMPLE: Could I just add one thing? In oncology anyway, the studies people do to confirm clinical benefit are often in a different stage of the disease. It would not be unusual, having given accelerated approval for second-line therapy, to reach the conclusion the drug is effective in this disease based on first-line studies which, as you know, are ongoing.

DR. D'AGOSTINO: What I wanted to follow up, we have some impressive data on the toxicities, as was pointed out, and you talk about looking at some of the time to progression of the disease and progression-free intervals, tumor response, the secondary variables.

Are we going to get caught in the dilemma that when you start looking at those variables, they show acceptance of a null hypothesis of equality, they don't show superiority, they don't show non-inferiority, so are you leading us in a path, or are we leading ourselves in a path that is really not going to resolve the issue of how to put

this data together outside of the toxicity, I think, which is quite superior.

DR. PAOLETTI: In designing and asking the questions, I think we outlined the problems here, how can we really address those problems. Here again, we would like to, when we get to the questions, talk about full approval of this drug also, so we are not just looking at accelerated approval here, and we would be happy with the conversation that has gone on to take a look at that question.

But here again, you know, these are very difficult problems to grapple with, how do we deal with them is very difficult to do, and I don't think there is a clear answer here.

DR. BRAWLEY: Dr. Cheson, then, Dr. George.

DR. CHESON: Since we are at least in part looking at this drug for consideration for accelerated approval, one of the requirements for this that Dr. Temple alluded to is that there be a program ongoing for confirmatory trials that will

address the safety and efficacy of this particular agent.

I am a lymphoma doc, so I don't really follow this lung cancer stuff, and I was wondering what sorts of trials are ongoing that may help resolve this issue, that can be done in the foreseeable future?

DR. PAZDUR: I believe there are at least three, and probably Paolo can address those, I did mention that in our introductory comments.

DR. PAOLETTI: Yes, we have one ongoing trial in second-line lung cancer, again an randomized trial, and we have two planned and one ready to start, again randomized trial in front-line lung cancer, where Alimta is combined with a platinum agent.

DR. BRAWLEY: Dr. George, then Ms. Ross.

DR. GEORGE: One quick question or one point on the accelerated approval issue. I have heard you say before, Rick, that accelerated approval is not a second-class approval, that is, it has to have the same level of evidence as you

would for full approval. It just means little different things.

That is not really why I raised my hand, but I felt we might want to discuss that some if we get to that point.

What I wanted to do is address a couple of quick points about the historical data and point out that I think it may be less reliable even than we have been talking about.

A couple of things. One is a minor sort of technical point that perhaps can be cleared up quickly. I was just reading the methods in the paper that reports the results, and it says there that survival time is censored with any subsequent chemotherapy, so that, in effect, crossovers would be censored, which would be kind of a bizarre thing to do, I think, in the statistical approach here.

We can argue about what it means to cross over and the effect on survival, but you don't usually censor it. That may be a misprint in the paper or misstatement, because I know it wasn't done here, but it does relate to how you--what you

are using as the historical control.

There was a 100 mg dose to start off, and that was on roughly the first half of the patients, and one interesting thing, and then they switched to 75 at the recommendation of the Data Safety Monitoring Board for the second half of the trial.

If you look closely at what the results were in the first half and the second half, let's just say look at the best supportive care in the 100 group, that is, the concurrent randomized group at that point, and look at what happened. There was no direct comparison, but eyeball it, compare that to the subsequent best supportive care in the 75 mg part of the trial, you will see that the best supportive care results got worse in the second half of the trial, maybe not significantly worse you can't do the test easily, just eyeball it, but clearly, if, say, the best supportive care group happened to be reversed, that is, the ones that got it in the first half or the ones you were actually looking at in the second half, your effect size, you estimate would be smaller, still with the same

kind of imprecision, but require then more difficulty in proving that you had non-inferiority.

So, I think this doesn't prove anything directly except that one small trial does create problems, and it may be even worse than has been indicated here.

DR. PAZDUR: To address Dr. George's question about secondhand approvals and level of confidence in the data, and I mentioned this in my introductory comments, most of the times when we are looking with this committee and also, if we take regulatory actions, without the committee's input, we have been looking at single-arm trials usually of 100 patients.

As I pointed out, even though this trial failed its primary endpoints, randomized trials always give you more information. We have randomized response rate information, we have randomized toxicity data. We can take a look albeit not through any formal non-inferiority mechanism, but at time to event and points, such as time to progression and survival.

Although we cannot with precision state what that non-inferiority is, I think we get some degree of confidence in making a regulatory decision here. We also have another approval of this drug and an unrelated disease albeit in mesothelioma, the first drug to have a survival effect in this disease.

We have Phase II trials that show activity also of this disease.

DR. BRAWLEY: I think we are morphing from questions to discussion here.

Dr Paoletti, do you have something specific?

DR. PAOLETTI: I think that Dr. Shepherd has something specific.

DR. SHEPHERD: I have to bear the responsibility, of course, for the TAX 317 trial. These little shoulders, though, have done a lot of best supportive care in placebo trials for this august group, which really cannot be done in the United States, and I would just like to remind you of that.

These are extremely difficult trials to do, and we unfortunately have to live with the trials that we have. Yes, the TAX 317 trial wasn't analyzes with censoring, and, yes, I recognize that there were differences in the survival of the best supportive care group in the second part of the trial, but I feel more comfortable with the follow-on of our BR21 trial that compared placebo to erlotinib in which once again we saw a no treatment survival that was really almost identical to the survival of the second half, not the first half, but the second half of the TAX 317 trial.

So, I think we can be comfortable with many hundreds of patients in the BR21 trial, what happens with no treatment, and I think that that supports the observations that we had in the TAX 317 trial.

DR. PAZDUR: To follow up on Dr. Shepherd's comment, we are aware there is a great deal of difficulty in dealing with placebo-controlled trials, A versus placebo. Those are being down outside of the United States primarily.

Alternatively, I think we need to keep in mind, as a field, that also then starts posing problems of constancy, what are the qualities of those patients going on, what are the supportive care, all Stage IV lung cancer metastatic disease is not the same once chemotherapy has started, may differ tremendously whether you are talking about Boston or Bosnia.

DR. SHEPHERD: Well, I can tell you that there is not a great difference between Boston and Toronto, and that when we looked actually at the Canadian patients in the NCI trial, which was an international trials, when we looked at Canada versus the rest of the world, it was actually a similar result.

DR. PAZDUR: I am just bringing that up as future concerns.

DR. SHEPHERD: I think polymorphisms and many other things may come into play when we are looking at different patient populations.

DR. BRAWLEY: Dr. Temple, you had a follow up?

DR. TEMPLE: Yes, I mean I know sometimes there is no choice because all you can do is compare one study with another, but if Dr. George points out that the first half of the study and the second half of the study are different, it is not that reassuring to learn that some other study was more like one-half than the other.

DR. BRAWLEY: Ms. Ross, you had a question?

MS. ROSS: I think I might have forgotten what the question was. I just want to again--indulge me as the patient advocate here, I am not a scientist--if FDA is not really sure and confident in the design of the non-inferiority trials, and if they approve that design for this sponsor to go forward, then, that question is moot. I mean they have done what they are supposed to do.

The question then becomes even if you are not satisfied, even if we accept you are not satisfied, doesn't the question then revolve around the risk-benefit ratio to the patient? Doesn't that take precedence at that point?

DR. BRAWLEY: Dr. Temple.

DR. TEMPLE: Well, we often agree with companies about a study design, but what determines whether data supporting approval arise from that design is the results.

So, there was hope that Alimta would actually be better. That was one of the hoped-for results. Had that occurred, we probably wouldn't even have brought it here.

It also is possible, I mean the best way to be non-inferior is to be slightly better, so that you are kind of leaning in a favorable direction, but don't quite show superiority.

Had that occurred, I mean it was a tiny bit better on median, but not better on hazard ratio, had that occurred, that would also be a relatively easy case. What you have got here is where they are sort of even when you looked at hazard ratios, and so we are expressing reservations about whether--not a conclusion, we are going to listen--we are expressing reservations about whether the Alimta has been shown to preserve

the modest but real survival effect of the control agent, which is still important.

MS. ROSS: Granted that is important, but even if you accept that there are going to be continued questions about that, what then is the next criteria?

DR. TEMPLE: The design really isn't the problem, the results are the issue. Nobody thinks it is a badly designed study, and as we have said repeatedly, the crossover is inevitable and unavoidable. Nobody doubts that anyone would not do that.

MS. ROSS: Right. So, then, what becomes the next criteria is my question.

DR. TEMPLE: That is sort of what we are asking about. If people were persuaded that the questions we have raised are not sufficient to raise doubts about whether it is, in fact, effective in the non-inferiority sense, then, it could be considered for full approval.

One of the options, though, created in, I don't know, 1996 or thereabouts, for diseases like

cancer was that if you have a surrogate you think is reasonable, and response rate has been considered a reasonable surrogate for clinical benefit, we can approve a drug if it has some advantage over other therapy even though true clinical benefit has not yet been demonstrated if we believe, for example, that it was clearly less toxic. That is what accelerated approval is for.

Accelerated approval is full approval, but on a condition that further studies be done, but the drug is sold and marketed, and so on.

MS. ROSS: There are other implications to accelerated approval versus full approval, too. Some of them put the patient in a very difficult position.

DR. TEMPLE: Say why?

MS. ROSS: There are other implications of accelerated approval versus full approval. I know you don't want to get into this today, but one of the implications is whether or not it is going to be covered.

DR. TEMPLE: I don't have the impression

that that is usually not covered. I know there has been discussions of some of those things. A lot of cancer drugs have been approved initially under the accelerated approval rule.

DR. PAZDUR: But I don't think we can go down that path and make any regulatory decision based on coverage, I am going to make that clear for all of the committee members and any voting or any decisionmaking that you make. That is a separate issue, can change today, can change tomorrow, can change every five minutes.

DR. BRAWLEY: But I should point out that most of the accelerated approval--at least all the accelerated approval drugs that I know of are covered by insurances including Medicare.

Dr. Bukowski.

DR. BUKOWSKI: There was mention made of another second-line trial with Alimta in lung cancer. Could you clarify or tell us what that trial consists of?

DR. PAOLETTI: Yes. This trial is ongoing and we are comparing two dose of Alimta, the 500

dose with a higher dose.

DR. BRAWLEY: Dr. D'Agostino.

DR. D'AGOSTINO: Just to go back, if I understand the question that was being raised, I mean in terms of my understanding of the approval process, if we are stuck on whether or not there is sufficient data for approval, we can't jump over it and use a different criteria, so I think we have to face the question do we think that there is enough data from this non-inferiority trial, and I think the questions about the historical database and the crossover still linger with us, and so the switch to the accelerated approval, which is quite viable here, and the data seems to line up quite nicely for that, I think is something that would be the switch as opposed to a risk-benefit and glossing over the non-inferiority trials discussion and problems.

DR. PAOLETTI: Dr. Shepherd, do you want to comment?

DR. SHEPHERD: I think that many of us feel that full approval is appropriate, but since

we have raised the issue of accelerated approval, there is another part of accelerated approval, and that is the unmet need.

We have an increasing population of patients who are receiving docetaxel first line. Its level of activity in the second line has led to randomized trials in the first line showing superiority, so docetaxel is being moved more and more into the first line in advanced disease, and the first line administered concurrently in locally advanced disease.

It has never been the practice with non-small cell lung cancer to re-treat patients in the second-line setting with the same agent. So, that leaves an increasing population of patients for whom there will be no approved second-line therapy.

DR. PAZDUR: Could I just interrupt you? I really don't follow your logic here, because if you are arguing accelerated approval versus full approval, the drug is available.

DR. SHEPHERD: Yes, well, I don't want to

either, and as a Canadian, I shouldn't be getting into reimbursement, but it is my understanding that it may not be reimbursed for non-indicated, not approved indications.

DR. BRAWLEY: I am going to take the Chair's prerogative here.

DR. SHEPHERD: And there is also the group with neuropathy that can't have the drug.

DR. BRAWLEY: I am hearing a lot of statements about reimbursement that I know are contrary to what I know to be true.

So, why don't we stop talking about reimbursement all together and let's get back to talking about the drug.

Dr. Levine.

DR. LEVINE: I have a very simplistic question to the statisticians. Because of the issues and difficulties with the crossover, what is scientifically wrong with just looking at data in those individuals who did not get further treatment? So, the study drug was 6.2 months versus 5 months in the docetaxel.

The time to tumor progression was the same, the response rate is the same, and if you just stop it at the end of all treatment, it seems to be quite equivalent. That is not hazard ratios, and so forth, but what is wrong with my thinking?

DR. BRAWLEY: Dr. Yong-Cheng Wang.

DR. WANG: That is a subgroup analysis. It doesn't show the whole population. So, subgroup analysis, the p-value is not interpretable.

DR. D'AGOSTINO: You have destroyed the randomization by doing that, so then from that point on, it is subgroup or it's sort of trying to intuit, and that is exactly nicely presented by Lilly in terms of trying to give us a feel for that, but as everybody is saying, we can't interpret the p-values anymore.

DR. BRAWLEY: Dr. Emerson.

DR. EMERSON: I would agree with the aspect of the subgroup analysis for several of your points, but not all of them. The aspect of looking at time to progression and defining progression as getting the same line there, but that is still a

randomized comparison, and there was equivalence on that endpoint.

For what it is worth, the subgroup analysis in which you say that you are just going to look at the group that never got the post-study chemotherapy is covered by that time-variant covariate analysis, and it was just looking at that 0.84 has a ratio that was in favor of Alimta, but again, the bias that creeps into that subset selection is too great.

DR. BRAWLEY: It's about noontime right now or five past noon. We have morphed into discussion away from questions. Are there any members of the committee with questions or things that they would like to discuss?

Yes, Ms. Haylock.

MS. HAYLOCK: You talked about different endpoints, and I was wondering where the issue of morbidity and mortality in terms of the symptoms--I think Dr. Levine mentioned the neutropenia, and I am thinking of the kinds of things that actually cause lung cancer patients to die, that may not be

directly related to tumor, but are related to the side effects of treatment, so I am wondering how you factor in the significance of the side effect profile of this drug versus the docetaxel.

DR. PAZDUR: Obviously, any regulatory decision is based on a risk-benefit analysis, but particularly in this situation, and the reason as we morph into the questions will be, the first question is asking does this drug have a more favorable toxicity profile.

The reason behind that from a regulatory point of view, in order to have an accelerated approval, you have to be better than available therapy, hence, a more favorable toxicity profile would encounter that requirement.

DR. BRAWLEY: Dr. Cheson.

DR. CHESON: I guess it's along the same lines. I would not like us to set a precedent for approving drugs vis-a-vis efficacy that don't meet either the primary or secondary endpoints.

We have had drugs in recent history that didn't meet the primary, met the secondary, and

didn't get approved, but as you said, its safety in this case may be the more compelling aspect of this drug, and I think that it is fairly impressive that it is safer, but I am certainly not convinced about any of the other endpoints, and I wouldn't like us to set that precedent or else we ought to start rethinking some other drugs.

DR. PAZDUR: So, Bruce, what you are saying is that no drug should be approved unless it meets its primary endpoint, and perhaps we should just refuse to file those applications?

DR. CHESON: No, I am saying if it doesn't meet the primary or the secondary endpoint of efficacy, then, it needs something else. In this case, it's the safety endpoint.

DR. PAZDUR: Don't throw the baby out with the bath water here, folks, okay? I think we have to take a look at how difficult doing clinical trials in oncology are, and I mentioned this before, that many areas do placebo-controlled trials. We can't do them especially in this situation where there is already approved drugs.

But this application is usually giving us more information than we get with a standard single-arm trial. Here, we have comparative toxicity data, we have comparative response rates. We could look, albeit we can't do formal non-inferiority analysis, at least a feeling of what is going on with time to progression endpoints far more superior than the standard single-arm trial that we get with an accelerated approval in a very refractory disease population.

DR. TEMPLE: Just one word about accelerated approval. When the whole idea was proposed, it recognized that by relying on a surrogate endpoint, quote, "reasonably likely to predict clinical benefit," there was a finite but real risk that you would eventually discover that there was not a clinical benefit.

So, that was considered an acceptable risk if you were getting something in return, and the something you could be getting in return is ability to treat a stage of disease that has no other treatment. That is the more usual one that comes

to the committee. But there is nothing incompatible with the idea that you would do it because you find a less toxic way of treating the same condition.

But there is clearly the possibility that we are going to turn out to be wrong, that it really will not have a benefit. You know, you have some track record with Alimta, so you are not too worried about that, we are not supposed to be too worried about that, but it could be. I mean that is part of the deal.

DR. BRAWLEY: Dr. Hussain.

DR. HUSSAIN: I have a comment and a question. The question is first. Was there a global quality of life tool done other than the symptoms and the lung cancer specific? That was one question, because I don't think we saw that global data, so that was one.

But if you don't mind while you are getting ready, I have a question to Dr. Pazdur and the group there.

I am looking at slide 35, and slide 35

talks about first-line monotherapy of Alimta, and talking about Alimta and docetaxel efficacy Phase II trials. There is really nothing in that slide that tells me a Phase III comparison should have been powered to look at a survival advantage.

Understanding these are all Phase II data, the responses are all over the place, overlapping, median survivals are overlapping, and that perhaps in avoiding problems like that, when you start in the beginning is look at the drug and see does this drug have any chance of proving superiority, and if it's not, then, that would be an unrealistic primary endpoint, and then power it for survival, but use a clinical benefit primary endpoint - is the patient going to live better, is their quality of life better, something meaningful, so that we don't end up in the predicament every single time you have very, very modest at best drugs.

DR. GRALLA: I would like to answer the global quality of life issue. I didn't present it for sake of time, but the LCSS, which is a validated instrument, includes quality of life

analysis, et cetera, did look at three summative items - global quality of life expressed by the patients, patient-expressed symptom distress, not just the symptoms, but how it affected them, and then their activity level or functional ability.

These were absolutely rock-on identical for each of the two arms of the study. Of course, as Dr. Shepherd presented to us from 317, there were significant advantages in performance status and already in ease of pain control that had come from the earlier placebo-controlled trial.

But actually, the symptom benefits that were seen here are greater and were slightly misrepresented unfortunately, with all due respect from the FDA presentation. It was stated that there was more weight loss for the group that got Alimta. This is, unfortunately, incorrect. This is not from the document, and is not correct.

The amount of weight loss of any grade of weight loss is 8.3 percent on the Alimta and 7.2 on docetaxel, exactly the same.

Could I see a slide that looks at severe

weight loss, which is more important? This is taken also, I borrowed it from Dr. Shepherd. If you look at the lefthand side of these bar graphs, we are looking at weight loss of more than 10 percent, which as Ms. Haylock has said, what are the toxicities that really, or the symptoms, or the problems that really threaten patients' lives, and a marked degree of weight loss does.

Again, all degree of weight loss was not different between the two, that is an incorrect statement.

If we look here, in TAX 317, the study that Dr. Shepherd talked about, and she presented the lefthand side of this slide, you can see that 25 percent of the patients getting just supportive care had a greater than 10 percent weight loss as opposed to 2 percent getting the docetaxel.

In this trial, the JMEI trial, which again is much larger, you had preservation of the lack of weight loss on the docetaxel arm, only 0.4 percent of patients had more than 10 percent, and you have the identical finding with the Alimta.

So, you have this finding of weight loss, a very important and easy to measure finding, and when you get into the PROs, you have patients expressing the same degree of quality of life, global quality of life and symptom distress.

DR. BRAWLEY: Thank you.

DR. EMERSON: The question about powering the study for survival versus for the secondary endpoints. If I could see slide 54. The key point I am trying to make here, of course, is that we have one hazard ratio here, and the confidence interval for that hazard ratio, and the question of superiority, non-inferiority, harm, or whatever, it is just a question of where we are along this number line in terms of the Alimta to docetaxel comparison.

So, in effect, when you are asking, well, we don't power the study for superiority, we power the study to be able to look at the secondary endpoints and be able to ensure that we still have reasonable comparability on survival. That really is the non-inferiority question.

The non-inferiority question is saying we are really going to be looking at some other endpoint, and we would like to make certain that our confidence interval is narrow enough to say that we are reasonably close.

Now, in this study, and if you will for a moment concede that it is somewhat relevant to the comparison to TAX 317, but I will come back to that in a second, if I could see slide 671.

This is the idea that in TAX 317, the hazard ratio was 0.56, the confidence interval was 0.35 to 0.88 over best supportive care. If we take the idea that what we had was two independent clinical trials and combining the estimates across those trials, from JMEI and using the TAX 317 data, we now estimate that the hazard ratio is 0.55 comparing Alimta to best supportive care, and the confidence interval is 0.33 and 0.90.

Why I just want to point this out is if that sample size in JMEI had become infinite with this particular hazard ratio estimate, the best we could have gotten is to that 0.35, 0.88.

So, everything revolves around the comparability of the TAX 317 and the JMEI docetaxel arms, which as we pointed out, had very similar baseline characteristics, very similar survival, and the major issue was the crossover study, which the best estimate we have is that there was no advantage due to the additional post-study chemotherapy.

DR. BRAWLEY: Dr. Temple.

DR. TEMPLE: Am I wrong in thinking that that analysis presumes that the docetaxel has an identical effect in both trials?

DR. EMERSON: No, you are not at all wrong. That analysis assumes that there is a comparable effect between the two. The percent retention analysis can be interpreted as a sensitivity analysis, that that might not be true.

DR. TEMPLE: But the critical assumption that the same exact effect showed up both times is the problem. That is why people do things like taking the 95 percent lower confidence interval.

DR. EMERSON: Except the percent retention

analysis can be interpreted as what contamination you might have a subpopulation in the JMEI study, in which the docetaxel effect was nonexistent, imagine the docetaxel was as good as placebo, and that interpretation placed on this Rothmann analysis, the percent retention, has an interpretation that says if you mixed up to 50 percent of patients in which docetaxel truly had no effect, but the other 50 percent docetaxel had the same effect that it had in the TAX 317 study, that this study would still support the idea that Alimta was--

DR. TEMPLE: But I wasn't asking about the Rothmann analysis, I was asking about the two numbers you put up, which make an assumption that few would believe is credible. That's all.

DR. BRAWLEY: This is how we are going to proceed. It is almost 12:20. Dr. D'Agostino has asked for the floor, I am going to give it to him. Then, I am going to ask if any other members of the committee would like to ask a question or make a statement.

Then, perhaps we will take a 10-minute break in lieu of going to lunch, and come back and morph into your questions.

Dr. D'Agostino.

DR. D'AGOSTINO: I will make it real fast. I wish Scott had not presented those last two slides, because that could have led us to three or four hours of discussion.

The question I really wanted to ask, and maybe we could take it up after the break, is I want to make sure we have some guidance in terms of it we go the accelerated approval, that we pick out variables that have this clinical benefit, because I am concerned that the data may or may not show that now. We can hold that.

DR. BRAWLEY: Well, the questions that we are asked don't discuss accelerated approval or approval, correct?

DR. PAZDUR: They do in a sense. First of all, the first question is based on a favorable toxicity profile. We have to answer that to do an accelerated approval because it has to have

advantage over available therapy.

The second question is given that, and given the uncertainty on the survival endpoint, an effect on the survival endpoint, do the surrogate endpoints of progression-free survival or predominantly response rate constitute an evidence for approval. That is where we are going.

The third question that I would like to ask, considering the considerable comments that have been made, was with the data presented and aware of the confounding effects that we have discussed with crossover, and also the single trial and estimation of the effect size being questioned, are people convinced of an effect on survival that would warrant full approval.

So, let's go a three-question approach here. The first two questions obviously are the accelerated approval, the last one, full approval.

DR. BRAWLEY: Any other questions from the committee members?

MS. ROSS: Just an observation, those are pretty loaded questions.

DR. BRAWLEY: Dr. Bukowski.

DR. BUKOWSKI: Dr. Gralla, can you clarify just for my edification Lung Cancer Symptom Index and the overall quality of life? They were similar between the two arms, Alimta and docetaxel, there were no differences between the arms?

DR. GRALLA: Correct.

DR. BRAWLEY: Anything else?

[No response.]

DR. BRAWLEY: With that, I have 12:22. I hate to do it this way, but let's get back together at 12:35 to tackle the FDA's questions.

[Break.]

ODAC Discussion

DR. BRAWLEY: If we can come back to order.

After this morning's presentations and the questions and discussion, we now have three questions in front of us. How we will work this is I will read the question, the questions are also up on the board here. We will have some discussion about each question, and then we will vote on the

question.

The first question is: Do you believe Alimta has a more favorable toxicity profile than docetaxel?

Any discuss on this issue? Yes, sir.

DR. GEORGE: Just a quick question. Because the weight loss issue came up, there seemed to be a difference between the FDA analysis and the sponsor.

Dr. Cohen, you didn't respond to that. Do you have anything?

DR. COHEN: I think that what I stated was correct and that the sponsor's summary documents and briefing documents I think would bear out that there is more weight loss associated with the Alimta than there is with docetaxel.

DR. BRAWLEY: Please identify yourself.

DR. NGUYEN: Binh Nguyen from Lilly.

Actually, in the briefing document on page 112 for the sponsor, the Table 5.1, the weight decreases 8.3 percent versus 7.2 percent, and I think that--I don't know exactly what the other

numbers come from.

DR. PERRY: I think the weight loss issue here is a real red herring. You have to remember that the people on the docetaxel arm got an enormous, bigger dose of decadron, which causes fluid retention, and therefore artificial weight gain. We are talking about 16 times the normal dose of prednisone equivalent that one makes per day versus 8 time in the Alimta arm.

DR. PAZDUR: Potentially, the fluid retention of the drug itself.

DR. PERRY: My point is I don't think weight loss is something we can measure, and if we have lean body estimates by radioactive potassium estimates, we could calculate whether this is real or not, but in the absence of it, I don't think weight loss is something we can discuss reasonably.

I do think that there is less neutropenia on the Alimta arm, so I think the answer to this question is yes.

DR. BRAWLEY: Any other discussion?

Dr. Levine.

DR. LEVINE: I would just like to make the point related to the corticosteroid, as well. The Alimta arm had greater rash and also greater nausea and vomiting, but the increased dose of steroids in the docetaxel arm could account for that conceivably as an anti-nausea drug, for example.

DR. BRAWLEY: Ms. Ross.

MS. ROSS: Thank you. I just want to make sure that everyone on the panel did have a chance to look at the letter you should have received in your packets from an actual lung cancer patient on Alimta.

She is not your typical patient because she has made it her business to find out everything that can be found out about the trials, drugs, lung cancer. In fact, she has her own on-line web site for this.

She makes it very, very clear that Alimta is far superior to docetaxel as far as side effects, delivery time is only 10 minutes versus hours, no neutropenia. She goes on and on, but I should definitely take a look at that letter

because it speaks to an actual experience, and not a number.

This is what I heard, too, from the many patients I polled on various lung cancer e-mail lists on the web.

DR. BRAWLEY: Thank you.

Any other comments from committee members?

[No response.]

DR. BRAWLEY: If we can go to the vote.

The question: Do you believe Alimta has a more favorable toxicity profile than docetaxel?

Dr. Cheson, if we can start with you.

DR. CHESON: Yes.

DR. PERRY: Yes.

DR. HUSSAIN: Yes.

DR. BRAWLEY: Yes.

DR. MORTIMER: Yes.

DR. RODRIGUEZ: Yes.

DR. DOROSHOW: Yes.

DR. BUKOWSKI: Yes.

DR. LEVINE: Yes.

DR. GEORGE: Yes.

DR. D'AGOSTINO: Yes.

MS. HAYLOCK: Yes.

MS. ROSS: Yes.

DR. GRILLO-LOPEZ: I don't have a vote, but if I had a vote, I would say yes.

DR. BRAWLEY: 13 to nothing yes, I believe is the answer. We have unanimity amongst the counters. That is a good thing.

Question No. 2: If the answer is yes, does the more favorable Alimta toxicity profile with supporting efficacy data on tumor response and PFS outweigh the uncertainty regarding loss of docetaxel survival effect by using Alimta?

Any discussion to the question? Does everybody understand what the question is?

MS. ROSS: I would like clarification, please.

DR. BRAWLEY: Dr. Pazdur.

DR. PAZDUR: Well, we have discussed and in the preamble to these questions, we have laid out that there have been or can be problems with the analysis of non-inferiority here. There are

problems with crossover that we have discussed. There are also issues in establishing historical data to measure the control effect.

Given these problems, there has to be some uncertainty about that effect. Given the information that you have on hand about the surrogate endpoints, that has to be weighed against this uncertainty here.

DR. TEMPLE: But if you are a person who doesn't believe there is any uncertainty, then, the answer could be yes for that reason. It is only if you do believe there is some uncertainty that this question is more interesting. But if you don't think there is a problem, then, your answer would, of course, be yes.

DR. BRAWLEY: Is there any further discussion? PFS, for those in the audience, is performance status? No, progression free survival. I am sorry, progression free survival.

DR. D'AGOSTINO: Now, we are not talking about superiority on this. No. Thank you.

DR. GEORGE: I guess that is similar to my

question. Does outweigh mean in the sense of being able to give accelerated approval?

DR. PAZDUR: This is an accelerated approval question.

DR. BRAWLEY: Ms. Ross.

MS. ROSS: Sorry to belabor this, but isn't the question assuming that we feel that there is uncertainty?

DR. PAZDUR: That is what Dr. Temple just mentioned, if you don't have any uncertainty.

DR. TEMPLE: If you believe the benefit in terms of toxicity outweighs whatever uncertainty there is, from zero to a lot, then, the answer is yes. But if you have no uncertainty, then, it obviously outweighs it.

MS. ROSS: And it is still yes.

DR. GRILLO-LOPEZ: I would like to ask for clarification since it looks like we are going to be voting accelerated approval or full approval. Since we have been today using the verb to morph, when does an accelerated approval morph into full approval?

DR. PAZDUR: When the sponsor completes usually the clinical trials that will confirm clinical benefit, and as pointed out, the sponsor has several trials that are ongoing. We had a meeting in March of 2003 to address this area. We wanted for sponsors that are going to receive accelerated approval for these trials to be ongoing, so we feel comfortable with this. It will be reflected in labeling also.

DR. BRAWLEY: Ms. Ross.

MS. ROSS: How long will it take the company to complete these additional trials?

DR. PAZDUR: The company will have to answer that question.

DR. PAOLETTI: The Phase III trials are ongoing, and at least for the first trial, one year, one year in-house, and then the other more, because you need to wait for survival. Probably we are talking between 2 to 4 years.

DR. PAZDUR: Sheila, the regulations stipulate that the sponsor should be doing these trials with "due diligence," so that would be left

up to the interpretation depending on the complexity of the trials, et cetera, that would enter into a completion date.

MS. ROSS: Thank you, Dr. Pazdur, I appreciate that, but I think the point here to keep in mind is that accelerated approval would be a further delay of 2 to 4 years.

DR. PAZDUR: No, the drug is approved, the drug is on the market being sold under accelerated approval.

DR. TEMPLE: That is why it is called accelerated.

DR. PAZDUR: It's approved.

MS. ROSS: You are not requiring them to complete the trials?

DR. PAZDUR: They are doing the trials. When those trials are approved, then, the accelerated approval will be converted to full approval, but the drug is on the market, they are charging for the drug. There is some limitations that they have to check advertising with D.D. Mack. There is a line stating in the indication that full

clinical benefit has not been established, but other than that, they are free to market the drug appropriately.

DR. BRAWLEY: Perhaps it would be useful if you were to name a couple of drugs that are currently on the market with accelerated approval.

DR. PAZDUR: Iressa is one, Velcade is one. We have many drugs, I just can't remember off the top of my head.

DR. TEMPLE: All the best drugs.

DR. PAZDUR: Bob said all the best drugs.

MS. ROSS: Thank you.

DR. PAZDUR: Remember, this drug also has full approval for mesothelioma.

DR. BRAWLEY: All right. Does the Alimta toxicity profile with supporting efficacy data on tumor response and progression-free survival outweigh the uncertainty regarding loss of docetaxel survival effect by using Alimta?

Let's start with Ms. Ross.

MS. ROSS: Yes.

DR. GRILLO-LOPEZ: If I were voting, I

would vote yes, but I would not have that vote interpreted as any way affecting a future vote on full approval.

DR. PAZDUR: We recognize that, and here again, obviously, if you vote on accelerated approval, that does not mean you could not vote for full approval. These are not mutually exclusive.

MS. HAYLOCK: Yes.

DR. D'AGOSTINO: Yes.

DR. GEORGE: Yes.

DR. LEVINE: Yes.

DR. BUKOWSKI: Yes.

DR. DOROSHOW: Yes.

DR. RODRIGUEZ: Yes.

DR. MORTIMER: Yes.

DR. BRAWLEY: Yes.

DR. HUSSAIN: Yes.

DR. PERRY: Yes.

DR. CHESON: Yeah. That is a yes with not much enthusiasm.

DR. PAZDUR: Is that a hanging chad?

[Laughter.]

DR. BRAWLEY: Thirteen to nothing yes.

The third question: Given the potential confounding effects of crossover and problems in estimating the control effect, is there a convincing effect on survival to warrant regular approval?

Dr. Hussain.

DR. HUSSAIN: So, Dr. Pazdur, could you please clarify what you mean by a convincing effect on survival, because if there was no difference in survival, what effect are we supposed to assess?

DR. PAZDUR: The effect. Remember we said that effect on the endpoint of survival can be two ways. One can see an improvement in survival or a non-inferiority effect on survival, and that would demonstrate with a reasonable amount of certainty--and I am using that word clinically--that a control effect has been preserved, that the effectiveness in your mind from a clinical judgment, that effect of docetaxel is preserved.

DR. BRAWLEY: Can we move on to

discussion?

Dr. D'Agostino.

DR. D'AGOSTINO: If we vote yes, then, we are saying that our doubts or the doubts that exist in this historical database in terms of its stability and precision is really not a concern to us. It is quite a precedent to move in this direction.

DR. BRAWLEY: Anyone else?

DR. PAZDUR: Most of the data, and perhaps the statisticians would like to comment on this in the statistical area, point to multiple trials having to be done to determine a control effect, to ensure issues of reproducibility, ascertainment of differences in patients, et cetera, that might be preserved.

Obviously, you don't need that, but it does set a different precedent in the sense that we have a very small trial here of only 50 patients in each arm.

DR. BRAWLEY: Yes, sir.

DR. GRILLO-LOPEZ: I actually sympathize

with the FDA in that I do understand the regulatory constraints that you have. On the other hand, I think that this may be a good precedent to set because as an oncology community, shouldn't we be seeking the earliest possible approval of drugs that do have clinical activity and efficacy even though it might not be as huge as we would like to see it.

But if that is accompanied by an acceptable lower toxicity profile, what harm is there in giving full approval to such drugs, that will then be made available to the oncology community, the cooperative groups, academic institutions, et cetera, to do the necessary combination studies to then find out what optimal combination they might best work under, and believe me, if they don't work, they will go down the drain. People will just not prescribe and use them.

DR. PAZDUR: Let me just clarify. When a drug receives accelerated approval, it is on the market, folks, okay. People could be doing

combinations, they could be charging for this drug. This is not a substandard approval here that we are talking about.

Studies go on with these drugs as they would if it were a regular approval.

DR. TEMPLE: Ordinarily, except for the case of accelerated approval, you are supposed to be able to conclude that the drug provides a clinical benefit. You know, you could ask why is the law written that way. Maybe you should just say it doesn't hurt you, and you should approve it if it doesn't hurt you enough, but that isn't what the law says. It says you have to have evidence of clinical benefit.

So, you know, you can think of that as a regulatory problem. Personally, I would think most people using drugs would want to know that the drug has a favorable effect, too, but whichever one it is, that is the difference.

Accelerated approval allows reliance on a surrogate for a benefit, and we obviously, based on our past history, and this committee, based on its

past history, believe that a response rate in a condition where there isn't anything else or the other things are bad, is a reasonable basis for accelerated approval. Nobody is really disputing that.

We are pretty happy with the outcome although it is worth noting the Europeans don't believe that is correct, and don't do that for the most part.

But the question posed here is can you go beyond that and say based on the data, that you are satisfied that it has some survival effect, such as the one equivalent to the control group or close to it.

DR. BRAWLEY: Dr. Levine.

DR. LEVINE: Just to clarify the meaning of Question 3, if we have already answered as we have on 1 and 2, and we answer no on 3, does that mean that you automatically are going toward accelerated approval?

DR. PAZDUR: Correct.

DR. LEVINE: Thank you.

DR. BRAWLEY: Dr. D'Agostino.

DR. D'AGOSTINO: Two comments. One, I didn't pick up on Dr. Pazdur's comment about in many of the non-inferiority trial settings, we tried to get an awful lot of historical database or large historical database, and tried to come to precise estimates of what the placebo or what the non-drug effect is, we don't really have that here.

The other comment is that there is a term they use in this field of non-inferiority trials of biocreep is if you allow this to sort of sneak in with a small database, then, the next one uses even a smaller database because it not pegged on this one here, so there is a real concern. It is not just a matter of being a cruel statistician.

DR. BRAWLEY: Ms. Ross.

MS. ROSS: Well, you could say that is why we are here. But I just want to make sure I understand. Maybe I should address this to the Chair, so I won't put anybody at FDA on the spot.

I would like to know what is the down side to accelerated approval vis-a-vis full approval?

DR. BRAWLEY: Well, I am going to answer the question since it was addressed to me, and then, Dr. Pazdur, you can tell me if I misstated this.

If it is accelerated approval, the company will be allowed to market the drug for its intended purpose that it was approved for, just as if it were a regular approval. If there is accelerated approval, the company takes what I will call a solemn vow that they will continue to do research, to do further development on the drug to prove survival advantage.

In terms of the availability of the drug to the public, there is no difference between the two. The real difference is with regular approval, the company does not have the government telling them that they have to continue doing work to develop the drug to truly determine if the drug has the benefit that we believe that it has.

Did I misstate that?

DR. PAZDUR: Pretty good, but the correct question, what is the up side of full approval?

You know, glasses are half-empty and half-full, Sheila. The up side is that the American public will have the confidence after these confirmatory studies are done that this is a real drug, the FDA will be monitoring whether these studies are done with "due diligence," and after the July meeting, we have been doing that with a greater degree of intensity.

So, there are advantages here that make sponsors be accountable to complete these studies. Yes, they could say they are going to do them, and, you know, a handshake rather than yes, you must do it, and we must see these study reports, we will be watching out for them.

I view this as an advantage, not necessarily a disadvantage or a down side. The only minor things, as I said, some of the marketing materials have to be looked at by our advertising department, and secondly, there is this line in the indication that states the clinical benefit has not been demonstrated.

DR. BRAWLEY: Yes. Keep in mind we are

giving advice to the FDA, we are not actually voting that the drug should be approved in any particular way. We are just giving advice to the FDA.

Is there a drug that has had accelerated approval and then has been removed? Dr. Bunn has been very patient.

DR. BUNN: I just want to clarify. For full approval, you have to prove a drug is safe and efficacious. You don't have to prove it is not inferior to something else. There is nothing in the regulation that has anything to do with non-inferiority. You have to prove it's safe and efficacious.

The clinical efficacy that is well accepted has been survival and patient reported outcomes, progression-free survival and response have usually been used as a surrogate. So, if you believe that there is a survival advantage over best supportive care or if you believe the patient reported outcome benefits over best supportive care, then, you could vote for full approval, that

it is safe and efficacious.

If you are uncertain about survival in patient reported outcomes, if you are quite certain about safety response rate and progression-free survival, then, you would vote for accelerated approval.

DR. PAZDUR: I think we have to take a look at exactly what safe and effective means and what effective means. It means that you have an effect on survival here in the situation that we are talking about.

As I stated before, the agency has looked at survival as clinical benefit. So, that endpoint, you have to demonstrate an effect on.

Now, most of the times we look at superiority trials, so there is no question you are better. Here, we have to say that you are non-inferior, so we are looking at a non-inferiority effect on that endpoint, and hence, we are talking about not losing a control effect here, part of the control effect.

DR. TEMPLE: Non-inferiority is the second

way to prove that you have an effect. You do that by gaining the ability to attribute the effect of the control to your drug by showing you are not too much worse.

If we were really insisting on a comparative efficacy requirement, we would have a much tighter demand for data. You wouldn't allow the new drug to be 50 percent worse on an important endpoint like survival. You would say 10 percent worse or 20 percent worse, which is, in fact, how antibiotics work. They have to rule out a difference that is considered clinically meaningful, and it is often quite small, 10 percent, something like that.

This is not comparability of effectiveness, it is non-inferiority as evidence that you have some effect, reasonable retention of the effect, 50 percent. It is not a very demanding standard.

DR. BRAWLEY: Ms. Haylock

MS. HAYLOCK: The concern about the history of the previous studies that were done, did

I mishear or am I correct that you said that that is the history, and you can't really go back and change that, nor can those studies be redone? So, for research, how does the company go about rectifying that or dealing with that question?

DR. PAZDUR: This is a problem, and that is why we are bringing this to this committee, and I think that this is going to be perhaps even an increasing problem with time. I made the reference to the fluorinated pyrimidines in the approval of capecitabine where we had 30 years of people doing 5FU-leucovorin versus 5FU, because nothing else was going on in the field.

That probably fortunately, won't be happening because we have a better and more aggressive environment in drug development now with newer agents and looking at different combinations.

So, that may be a problem. You can have, and perhaps Bob wants to talk about it, you know, a single study if it was a very large study and we would provide a different statistical approach to that.

DR. TEMPLE: I just wanted to observe this is a general problem. There are very few people in which anybody would let you do a placebo-controlled, long-term, lipid-lowering study anymore. You could do add-on studies, add something new to something that existed before, because that hasn't been tested, but wherever there is established therapy, people are properly reluctant to leave--for a life-threatening disease--people are quite properly reluctant to leave people off it.

So, the question is how do you get there. Well, you can do an add-on study, as Rick said in his opening remarks, that is easy. Those are superiority studies and easy to interpret. But exactly how to do these persuasively, especially when there is only one or a small number of studies, is one of the biggest current problems in drug development. It is very thorny, you don't want to make a mistake.

You don't want to overdo it, but you don't want to approve something that doesn't work either.

So, good luck.

DR. BRAWLEY: Ms. Ross, did you have another question?

MS. ROSS: No.

DR. BRAWLEY: Anybody else? Okay.

Given the potential confounding effects of crossover and problems in estimating the control effect, is there a convincing effect on survival to warrant regular approval?

Let's start with Dr. Cheson.

DR. CHESON: No.

DR. PERRY: Yes.

DR. HUSSAIN: No.

DR. BRAWLEY: No.

DR. MORTIMER: Yes.

DR. RODRIGUEZ: No.

DR. DOROSHOW: Yes.

DR. BUKOWSKI: No.

DR. LEVINE: No.

DR. GEORGE: No.

DR. D'AGOSTINO: No.

MS. HAYLOCK: Yes.

DR. GRILLO-LOPEZ: If I were to vote, I would say yes.

MS. ROSS: Yes.

DR. BRAWLEY: The vote is 8 no, 5 yes.

Are there any other issues for the committee from the Food and Drug Administration?

DR. PAZDUR: No, just on the part of the FDA, we would like to thank you for your deliberations and also Eli Lilly for their participation during the NDA review process. We found it was a very good process and a very communicative process.

We brought this application here because there were problems. We expect these problems to be with other applications, and I think it needed the light of day to really expose the problems of the control effect and obviously crossover and non-inferiority trials for others to consider before they embark on this venture.

Thank you.

DR. BRAWLEY: With that, I would like to thank Eli Lilly and thank the Food and Drug

Administration, and we are adjourned.

[Whereupon, at 1:11 p.m., the meeting adjourned.]